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Award Number: DAMD17-96-1-6294

TITLE: Stress and Immunity Breast Cancer Project

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CONTRACTING ORGANIZATION:

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REPORT DATE: September 2001

TYPE OF REPORT: Final

PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

DISTRIBUTION STATEMENT: Approved for Public Release;
Distribution Unlimited

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REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 074-0188

1. AGENCY USE ONLY (Leave blank)	2. REPORT DATE	3. REPORT TYPE AND DATES COVERED
	September 2001	Final (15 Aug 96 -14 Aug 01)

4. TITLE AND SUBTITLE
Stress and Immunity Breast Cancer Project

5. FUNDING NUMBERS
DAMD17-96-1-6294

6. AUTHOR(S)
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7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)
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8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)
U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

10. SPONSORING / MONITORING AGENCY REPORT NUMBER

11. SUPPLEMENTARY NOTES

12a. DISTRIBUTION / AVAILABILITY STATEMENT
Approved for Public Release; Distribution Unlimited

12b. DISTRIBUTION CODE

13. ABSTRACT ***(Maximum 200 Words)***

A biobehavioral model of cancer stress and disease course was proposed (see Andersen, Kiecolt Glaser, & Glaser, 1994). We are testing the model with a clinical trial: 228 women with stage II or III breast cancer were randomized between assessment and intervention or assessment only (control) study arms. In addition to documenting the quality of life benefits of a psychological intervention, this study provides an experimental test of the psychological and behavioral variables which may influence health outcomes directly. Further, we test specific mechanisms--alteration in immune and endocrine functions--to achieve beneficial health effects for women with breast cancer. Our data indicate that psychological stress is instrumental in increasing a woman's risk for lower quality of life and depressive symptoms following surgery (Golden-Kreutz et al., under review; Golden-Kreutz et al., under review), and stress due to breast cancer surgery produces sexual and body image difficulties (Yurek et al, 2000). Further, psychological stress has a down regulating effect on immunity (Andersen et al., 1998). However, data suggest that the psychological intervention results in lower stress, improved quality of life, reductions in negative health behaviors, and enhanced immunity (t cell blastogenesis) (Andersen et al., in prep.).

14. SUBJECT TERMS
Breast cancer, psychological, behavioral

15. NUMBER OF PAGES
41

16. PRICE CODE

17. SECURITY CLASSIFICATION OF REPORT	18. SECURITY CLASSIFICATION OF THIS PAGE	19. SECURITY CLASSIFICATION OF ABSTRACT	20. LIMITATION OF ABSTRACT
Unclassified	Unclassified	Unclassified	Unlimited

Table of Contents

Andersen, B.L., Farrar, W.B., Golden-Kreutz, D., Kutz, L.A., MacCallum, R., Courtney, M.E., & Glaser, R. (1998). Stress and immune responses following surgical treatment of regional breast cancer. *Journal of the National Cancer Institute,* 90 (1), 30-36.

Yurek, D., Farrar, W., & Andersen, B.L. (2000). Breast cancer surgery: Comparing surgical groups and determining individual differences in post operative sexuality and body change stress. *Journal of Consulting and Clinical Psychology, 68,* 697-709.

4. INTRODUCTION

We have proposed a biobehavioral model of cancer stress and disease course (see Andersen, Kiecolt-Glaser, & Glaser, 1994, for a full discussion). The model identifies the psychological and behavioral factors and the biologic mechanisms by which health outcomes and cancer progression might be influenced. This model provides the conceptual basis for the proposed research . The present study is a randomized clinical trial testing the model. 228 women with stage II or III breast cancer who have been diagnosed and surgically treated were randomized between two conditions: (1) assessment and intervention, or (2) assessment only (control). In addition to documenting the quality of life benefits of a psychological intervention, this study provides an experimental test of the psychological and behavioral variables which may influence health outcomes directly. Further, we test specific mechanisms--alteration in immune and endocrine functions--to achieve beneficial health effects for women with breast cancer.

5. BODY

Army funding in 1996 enabled this large, important effort to continue beyond the pilot phase. Full funding enabled us to move aggressively ahead on subject accrual, complete the backlog of previously unfunded tasks, and, importantly, expand the biologic aspects of the project. The schematic for the study is provided in Table 1 below. Three types of preliminary data are provided, per the statement of work: Task 1 (Recruitment), Task 2 (Intervention Groups), Task 3 and 4 (Data Collection and Analysis).

Because of this success, we have recently recieved (7/1/01) a grant from the National Cancer Institute to extend the follow up through years 6-10. While this will be extremely helpful, additional funds will need to be secured as the budget is insufficient to cover all the anticipated assessments.

Table 1. Schematic diagram of the research design for subjects across the 5 years of study participation.

	YEAR 1				YEARS 2-5	
Dx./Ca. Trt	Follow up (months)				Cont. Follow up (months)	
Grp	0	4	8	12	6	12
1	x----------Inten----------x---Maintenance-x--Maintenance------x				x	x
2	x----------None----------x--------None------ x---------None--------x				x	x

Note: *Dx.* = Cancer diagnosis and *Ca.Trt.* = Beginning of initial cancer treatment; Inten(sive) = Weekly (x18) intervention sessions with reliability/validity checks on intervention integrity; Maintenance = Monthly (x8) intervention sessions with reliability/validity checks; *x* = Psychological, health behavior, compliance, and immune and endocrine assessments and disease endpoints.

Task 1: Recruitment

In August 2000, our accrual goal (N = 200) was met and exceeded with a final N of 228. During the years of accrual, refusal rates were calculated each six months and ranged from 30% to 75%, with the overall rate being 52%. Variability was due to such factors as the following: personal effectiveness of the research staff member approaching the patients, level of involvement of the physician staff, physician turnover, and relocation of the breast clinic from the main campus to a community location which, during the transition year, resulted in medical staff disruption and turnover. Most of these factors are not under study control, and, indeed, represent the challenges of accrual of large numbers of patients for multi-year clinical trials in today's medical environment. We were also recruiting women for a labor intensive, 5 year commitment, and approaching women on what many described as

'the worst days of my life.'

We gathered extensive process and descriptive data regarding refusal. Women indicated their reasons for refusal and the four most common were too far to drive (25%; accrual radius was 0-75 miles from Columbus, OH), do not have the time (20%), not interested (17%), and other (17%), with the other response scattered across the remaining items, which included too much stress (9%) and not under stress (2%). As was possible, a demographic and disease/treatment profile was obtained and as elaborated below, there is no discernable disease-relevant bias in the sample. Chi-Square or ANOVA's contrasting Acceptors vs. Refusers were conducted; to be conservative, Bonferroni corrections were not made. Regarding demographics, the groups did not significantly differ on race or marital status. Regarding disease and prognostic characteristics, the groups did not significantly differ on menopausal status, hormone receptor status, stage of disease, or number of positive nodes. Regarding received/anticipated cancer treatment, the groups did not significantly differ on extent of surgery or receipt of breast reconstruction, or recommendations for chemo-, radiation, or hormonal therapies. The only difference found between groups was age ($p = .034$), with the study participants being two years younger ($M = 50.67$) than the refusers ($M = 52.83$). As the samples were statistically equivalent on all other variables (including menopausal status which is correlated with age) it is unlikely that the two year age difference has any psychological, behavioral, or medical prognostic importance.

Below in Table 2 is a tally for the accrual and resulting numbers of psychological/medical/immune assessments for grant years 1-5. Per subject, there are 4 assessments during year 1 of participation (e.g. 45 Ss x 4 = 180) and 2 assessments/year for years 2-5 (e.g. 45 Ss x 2 = 90) of participation. There were 228 Ss accrued.

Table 2. Final actual and actual and projected number of assessments to be completed.

Grant year	**Accrual**	**Assessments by Accrual Year**					**Assessment Summary**
		Pilot	**1**	**2**	**3**	**4**	**N/year**
Pilot	45	180	___	___	___	___	180
1st year	45	90	180	___	___	___	270
2nd year	45	90	90	180	___	___	360
3rd year	45	90	90	90	180	___	450
4th year	48	90	90	90	90	204	564
5th year	--	--	90	90	90	102	372

With any longitudinal study retention can be a challenge, and if low, it can pose a major threat to the reliability, validity, and interpretation of findings. Indeed, other intervention studies have reported dropout rates ranging from 18 to 44% (i.e. 24 % in Edelman et al 1999; 44% in Ilnyckyj et al, 1994; 18% in Fawzy et al., 1990 a&b) with much shorter periods of follow up (6 months or less). Also, dropouts often come in disproportionate numbers from the control group (e.g. 100% in Fawzy et al., 1990 a & b were controls). Although our data will be analyzed according to *intent to treat*, high retention has been a day-in and day-out goal for this project.

The dropout rate is an exceptionally low 9% after an average of 35 months of continuous participation. The final rate after five years of follow up will likely remain low as only 25% of the dropouts have occurred within years 2-5

of their participation. Importantly, dropouts are approximately evenly distributed, with 10 of 23 (43%) from the intervention arm and 57% from the assessment arm. Also, data suggest that dropout is not a negative response to study participation, per se, but part of a general pattern of non compliance, i.e. A woman does not return for medical follow up, as this is the case for approximately 50% of our dropouts.

Task 2: Intervention Group and Study Arms

Thirteen of 13 cohorts of intervention groups have been completed; the final cohort was completed on February 1, 2001. Randomization was stratified by prognostic factors, three disease-relevant and one psychosocial: a) nodal status/tumor size and ± bone marrow transplant (BMT) (4 levels: negative nodes but tumor > 2 cm, 1-3 positive nodes, 4+ nodes w/BMT, 4+ nodes w/o BMT); b) hormone receptor status (2 levels: positive vs. negative); c) menopausal status (2 levels: pre/peri- vs. postmenopausal); and, d) spouse support status (2 levels: spouse/spouse equivalent vs. none). We used White and Freedman's (1978) minimization method to allocate patients to the treatment groups. A biased coin, weighted in favor of the group with fewer patients, was used to make the assignment. This randomization strategy was extremely effective, resulting in minimal differences between groups on sociodemographic, disease, cancer treatment, and medical evaluation variables (see Table 3 below), or psychological, behavioral, endocrine, immune variables (see Table 3). Data analyses below are organized by tests of components of the Model and then tests of the effectiveness of the psychological intervention. Here we provide selected analyses and with limited detail in some cases.

Task 3 and 4: Data Collection and Analysis

Testing Components of the Biobehavioral Model

A. The Cancer Stressor and the Context of Life Stress

The data in Table 4 indicate that the study participants, as a group, reported considerable psychological stress as they entered the trial. Concerning stressful life events, 50% of the sample had experienced the death or serious illness of a relative or close friend, 24% had major financial difficulties, 20% reported divorce/breakup of relationships with family or close friends, and 18% reported major conflicts with their children/grandchildren in the 12 months prior to diagnosis. In terms of global stress, scores on the Perceived Stress Scale (Cohen et al. 1983) of 18.37 are nearly 1 SD above the mean for adults (M= 13.02, Cohen & Williamson, 1988). Concerning stress due to cancer, per se, the Impact of Events (IES; Horowitz et al. 1979) group mean scores (Total M = 26.01) and subscales (Avoidance M = 12.41, Intrusion M = 12.81) are in the clinically significant range (I.e. Total M's > 19; Horowitz, Field, & Classen, 1993) and they are approximately 1 SD higher than those reported for other breast cancer patient samples (e.g. M = 16.4 in Cordova et al., 1995).

B. Stress and Quality of Life (QoL)

1. Golden-Kreutz, D., Thornton, L., Frierson, G., Lawrence, H., Carpenter, K.M., Shelby, R.A., Wells, S., & Andersen, B.L. (Under review). Global stress at cancer diagnosis/surgery -predicts quality of life in wmen with breast cancer. The Biobehavioral Model predicts that the stress surrounding the diagnosis and treatment of cancer will adversely impact quality of life. This relationship was prospectively tested in 217 women, initially assessed after breast cancer diagnosis/surgery and prior to adjuvant treatment and then reassessed at 4- (during adjuvant tretment) and 12-months (post-adjuvant treatment). Stress was operationalized with measures of stressful life events, stress specific to cancer (IES; Horowitz, Wilner, & Alvarez, 1979), and global stress (PSS; Cohen, Kamarck, & Mermelstein, 1983). Using Hierarchical Multiple Regressions, the variance accounted for ranged from 12% to 39% in physical and 19% to 59% in psychological QoL ourcomes (SF-36). Global stress (in contrast to life events and cancer specific stress) significantly predicted both QoL outcomes at all time-pooints. These findings substantiate the relationship between levels of innitial stress and later QoL outcomes as predicted by the Biobehavioral Model.

Table 3. Baseline equivalence of study arms on demographic, prognostic, recommended cancer treatment, and medical evaluation of system variables. Means and standard deviations and/or percentages are provided.

Area	N	Total Group (N = 228)	Study Arm	
			Intervention (n = 114)	Assessment-Only (n = 114)
Sociodemographic				
Age	228	50.78 (10.72)	51.13 (10.83)	50.44 (10.65)
Race (Caucasian, Af Am,Other)	228	90% 10% 1%	90% 9% 1%	90% 9% 1%
Education (yrs)*	228	14.76 (2.74)	15.18 (2.84)	14.33 (2.58)
Family Income (K/Year)	212	67.66 (70.84)	69.92 (55.04)	65.36 (84.17)
Marital Status (Married vs Other)	228	67%	67%	66%
Significant Other (Y/N)	228	73%	75%	71%
Prognostic				
Stage (II vs III)	228	90%	89%	92%
Nodes (number)	228	3.10 (5.45)	3.15 (5.66)	3.04 (5.25)
Tumor size (cm.)	288	3.04 (1.83)	3.12 (1.84)	2.96 (1.83)
ER/PR (% positive)	228	69%	68%	70%
Menopausal status (%Pre/peri)	228	54%	55%	52%
Treatment Recommended				
Surgery (Lump. vs Mast/other)	228	43%	44%	42%
Days since surgery	228	37.30 (19.28)	36.78 (21.35)	37.88 (17.01)
Chemotherapy (% treated & dose)	188	84%	84%	83%
Adriamycin	188	69%	72%	67%
		37.85 (9.15)	39.24 (10.29)	36.41 (7.63)
Cytoxin	187	81%	80%	82%
		520.97 (417.14)	571.85 (503.19)	473.36 (312.18)
Methotrexate	28	13%	11%	16%
		40.69 (26.05)	40.96 (18.76)	40.52 (30.68)
5-FU	41	21%	20%	22%
		446.40 (119.31)	448.58 (121.35)	444.43 (120.39)
Taxol	48	18%	20%	16%
		132.73 (43.24)	34.98 (53.75)	29.88 (26.01)
Hormonal therapy	228	78%	76%	81%
Radiation therapy	228	53%	55%	51%
Medical Evaluation of Systems				
Karnofsky Rating*	228	85.09 (7.99)	83.74 (8.73)	86.46 (6.93)
SWOG[a] Circulatory	228	1.34 (1.84)	1.36 (1.95)	1.32 (1.73)
SWOG Cardiac	228	.37 (.94)	.35 (.95)	.37 (.93)
SWOG Gastrointestinal	228	1.26 (1.60)	1.21 (1.55)	1.31 (1.73)
SWOG CNS	228	2.40 (1.70)	2.47 (1.80)	2.32 (1.60)
SWOG Renal/Bladder	228	.61 (1.3)	.55 (1.3)	.68 (1.3)
SWOG Composite Score	228	16.61 (8.80)	16.91 (8.75)	16.31 (8.87)

* $p < .05$; [a] denotes Southwest Oncology Group toxicity evaluation criteria

Table 4. Baseline equivalence of study arms on the Biobehavioral Model variables. Means and standard deviations and/or percentages are provided.

Construct	N	Total Group (N = 228)	Study Arm: Intervention (n = 114)	Study Arm: Assessment-only (n = 114)
Stress				
Perceived Stress Scale	228	18.37 (6.99)	18.67 (7.07)	18.07 (6.92)
Impact of Events Scale	228	26.01 (14.42)	26.08 (14.36)	25.95 (14.54)
Life Events	228	1.30 (1.12)	1.34 (1.13)	1.26 (1.11)
Quality of Life				
SF-36 Physical Functioning Composite	228	40.39 (7.99)	40.26 (7.72)	40.52 (8.28)
SF-36 Mental Health Composite	228	42.60 (11.43)	41.44 (11.64)	43.79 (11.13)
Emotional Adjustment/Distress				
Depression: CESD (short form)	228	6.03 (3.70)	6.08 (3.95)	5.99 (3.45)
POMS Total Mood Disturbance	228	35.75 (34.07)	40.06 (35.30)	31.43 (32.36)
Social Adjustment				
Perceived Support - Family	228	16.44 (4.27)	16.30 (4.33)	16.57 (4.22)
Perceived Support - Friends**	228	16.86 (3.46)	17.44 (3.05)	16.25 (3.76)
Social Network Index	228	3.12 (.84)	3.13 (.81)	3.10 (.87)
DAS Marital Satisfaction*	180	3.69 (1.38)	3.48 (1.44)	3.92 (1.29)
QRI Relationship Depth	179	2.53 (.65)	2.56 (.62)	2.50 (.68)
Breast Specific Component				
Previous Sexual Activity	180	4.16 (1.90)	4.01 (1.90)	4.32 (1.89)
Body Satisfaction	228	34.77 (8.14)	34.48 (7.96)	35.06 (8.35)
Breast Satisfaction	228	6.30 (2.12)	6.55 (2.14)	6.04 (2.08)
Health Behaviors				
Positive				
Diet: Food Habits Questionnaire	228	2.51 (.49)	2.53 (.47)	2.49 (.51)
Exercise: Daily	138	38.80 (14.20)	38.11 (9.76)	39.42 (17.28)
Exercise: Weekly	131	17.31 (27.09)	15.70 (24.85)	18.74 (29.06)
Exercise: Past 3 Months	228	203.59 (492.25)	194.48 (388.72)	212.78(579.90)
Exercise: Baecke	80	7.07 (1.23)	7.17 (1.33)	6.9 (1.10)
Negative				
Alcohol: MAST (short form)	228	.81 (1.57)	.79 (1.93)	.82 (1.09)
Smoking: Status (y/n)	228	10%	8%	12%
Compliance				
Chemotherapy: Y/N	188	84%	86%	83%
Radiation: Y/N	188	53%	55%	51%
Tamoxifen: Y/N	188	78%	76%	81%

continued on next page

Table 4 continued: Baseline equivalence of study arms on the Biobehavioral Model variables. Means and standard deviations and/or percentages are provided.

Construct	N	Total Group (N = 228)	Study Arm: Intervention (n = 114)	Study Arm: Assessment-only (n = 114)
Endocrine				
Cortisol: serum	166	11.16 (5.03)	11.32 (5.10)	11.00 (4.99)
Cortisol: salivary	46	47.46 (49.89)	62.61 (48.95)	36.79 (48.62)
ACTH	25	13.40 (7.78)	12.47 (10.40)	13.84 (6.54)
Epinephrine	79	30.18 (19.34)	28.81 (15.86)	31.11 (21.51)
Norepinephrine	80	295.26 (105.41)	304.40(120.67)	288.51(93.39)
Human Growth Hormone	120	1.04 (1.44)	1.24 (1.58)	.82 (1.24)
Prolactin	121	24.45 (33.31)	29.40 (39.47)	18.89 (23.77)
Immunity				
Cell subset numbers: NK cell %[a]	228	13.29 (6.86)	12.94 (7.32)	13.64 (6.37)
NK cell lysis (50:1)[b]	228	47.98 (18.83)	47.98 (18.92)	47.98 (18.83)
MAb T3 blasto (64:1)[c]	214	.45 (.27)	.42 (.27)	.47 (.27)
PHA (5)[d]	216	.45 (.23)	.44 (.23)	.46 (.24)
Con A (5)[e]	216	.38 (.20)	.37 (.20)	.40 (.19)
IL-2 (25:1)[f]	55	2.91 (5.18)	1.90 (2.18)	4.42 (7.60)
rIFNγ (25:1)[g]	102	2.50 (4.58)	1.75 (1.04)	3.09 (6.02)
Disease Course				
Recurrence (Yes/%)	228	34 (15%)	16 (14%)	18 (16%)
Disease Free Interval (months)	228	27.2 (12.2)	27.8 (12.73)	26.8 (12.0)
Survival (Yes/%)	228	220 (92%)	112 (97%)	108 (94%)
Cause of Death:				
Cancer	228	5	1	4
Other Causes	228	6	3	3

* $p < .05$; ** $p < .01$

[a] No differences were found between groups for other cell subsets including T3, T4, and T8 percent.

[b] NK cell lysis at E:T ratio of 50:1. No differences for other E:T ratios including 100:1, 25:1, 12.5:1, 6.25:1, 3.125:1.

[c] T3 Mab blastogenesis at mitogen concentration of 64:1. No differences for other concentrations including 128:1 and 32:1.

[d] Data for PHA blastogenesis at mitogen concentration of 5:1. No differences for other concentrations including 10:1 and 2.5:1.

[e] Data for ConA blastogenesis at mitogen concentration of 5:1. No differences for other concentrations including 10:1 and 2.5:1.

[f] Data for IL-2 at E:T ratio of 25:1. No differences for other E:T ratios including 50:1, 12.5:1, 6.25:1, and 3.125:1

[g] Data for rIFNγ at E:T ratio of 25:1. No differences for other E:T ratios including 50:1, 12.5:1, 6.25:1, and 3.125.

2. Golden-Kreutz, D., & Andersen, B.L. (Under review, abstract). Correleates of depressive symptoms in women with regional breast cancer: Examining objective versus subjective stress after surgery. The relationship of objective stressors (life events) and subjective (perceived) stress to depressive symptoms was examined. These relationships were explored in stressed individuals, potentially vulnerable to the experience of depressive symptoms, namely 210 women recently diagnosed and surgically treated for regional (Stage II or III) breast cancer. Analyses controlled for potentially relevant correlates including sociodemographic, disease, and personality factors. Using Hierarchical Multiple Regression, 53% of the variance in depressive symptoms was accounted for by control variables (race and neuroticism), objective stressor (major financial difficulty), and perceptions of cancer stress (IES), and global stress (PSS). These findings provide needed information regarding the correlates of depressive symptoms in women with regional breast cancer for whom the risk of recurrence is significant.

3. Yurek, D.A., Farrar, W.H., & Andersen, B.L. (2000). Breast cancer surgery: Comparing surgical groups and determining individual differences in post operative sexuality and body change stress. *Journal of Consulting and Clinical Psychology, 68,* 697-709. (Abstract). Women diagnosed and surgically treated for regional breast cancer (N = 190) were studied in the early post surgical period to determine the sexual and body change sequelae for women receiving modified radical mastectomy with breast reconstruction (MRMw/R) in comparison to the sequelae for women receiving breast conserving therapy (BCT) or modified radical mastectomy without breast reconstruction (MRM). The sexuality pattern for women receiving reconstructive surgery (MRMw/R) was one that was significantly different--with lower rates of activity and fewer signs of sexual responsiveness--than that for women in either of the other groups. Testing a model for the prediction of risk for sexual morbidity (Andersen, 1994), regression analyses controlling for menopausal status, prior sexual behavior, and extent of disease and treatment revealed that individual differences in sexual self schema (Andersen & Cyranowski, 1994) were related to both sexual and body change stress outcomes. These data indicate that breast reconstruction is not a panacea for the sexual disruption and body change concerns arising after surgery for breast cancer.

C. Cancer Stress and Immunity

Andersen, B.L., Farrar, W.B., Golden-Kreutz, D., Kutz, L.A., MacCallum, R., Courtney, M.E., & Glaser, R. (1998). Stress and immune responses following surgical treatment of regional breast cancer. *Journal of the National Cancer Institute,* 90 (1), 30-36. (Abstract). We examined the relationship between stress and several aspects of the cellular immune response in the context of the diagnosis of breast cancer and the post surgery period. Women (N = 116; 50% of the study sample) newly diagnosed and surgically treated for Stage II (70%) or III (30%) invasive breast cancer participated. Prior to beginning adjuvant therapy, all completed a self report measure assessing stress about the cancer experience (Impact of Events Scale) and provided a 60cc blood sample. A panel of natural killer (NK) cell and T-cell assays were conducted: 1) NK cell lysis; 2) the response of NK cells to recombinant gamma interferon (rIFN-g) and recombinant interleukin-2 (rIL-2); 3) blastogenic response of peripheral blood leukocytes (PBLs) to phytohemagglutinin A (PHA) and concanavalin A (ConA) and the proliferative response of PBLs to a monoclonal antibody (MAb) to the t-cell receptor (T3). Multiple regression models were used to test the contribution of psychological stress in predicting immune function. We hypothesized a negative relationship between stress and immunity, and expected this relationship to be replicated between assays and within a single assay [i.e. replicated across effector to target (E:T) cell ratios for NK cell lysis, for example]. All regression equations controlled for variables which might also be expected to exert short or long term effects on these responses, such as age, stage of disease, and length of time of surgical recovery, and ruled out other potentially confounding variables (e.g. nutritional status) that might also be influential. These controls reduced the plausibility of alternative, rival hypotheses for the findings. Significant effects were found and replicated between and within assays, including the following: 1) stress significantly ($p < .05$) predicted NK cell lysis; 2) stress significantly ($p < .01$) predicted the response of NK cells to rIFN-g, replicated across 4 E:T ratios; 3) stress significantly predicted the response of PBLs to ConA ($p < .05$) and PHA ($p < .05$), and the proliferative response to the T3 MAb ($p < .05$). The data show that the physiologic effects of stress inhibited a panel of cellular immune responses, including cancer-relevant NK cell cytotoxicity and T cell responses.

Biobehavioral Effects of the Intervention

A. Intervention Compliance and Data Analysis Overview

All individuals randomized to the intervention arm have completed both intensive (4 month) and maintenance phases (12 month). Participation in the intervention arm has been high, with 81% of the individuals defined as completers (i.e. receive ≥ 10 of 18 intensive sessions) and 19% defined as non completers. Participants completed the majority of the intervention sessions (either directly with group attendance or indirectly with telephone follow ups for missed sessions), a mean of 17 of 18 intensive sessions and 7 of 8 maintenance sessions. The data presented are analyzed according to *intent to treat,* i.e. data from intervention completers as well as noncompleter/dropouts are included.

For the majority of the analyses, a 2 (Group: Intervention vs. Assessment) x 2 (Time: Initial vs. 4 months) repeated measures ANOVA or ANCOVA model was used, with the hypotheses centering on significant Group x Time interactions. That is, the intervention group is predicted to have lower stress, enhanced quality of life, more positive and fewer negative health behaviors, better compliance, and enhanced immune responses. Data for the initial and 4 month assessment includes cohorts 1-13, with approximately n = xxx for the intervention group and n = xxx for the assessment only group. Longer follow up is needed for some variables (e.g. physical activity, compliance), and so data analyses are not yet complete. As the trial is still in progress, these data are preliminary.

B. Stress and Immunity

Andersen, B.L., Carson, W., Glaser, R., Golden-Kreutz, D., & Crespin, T. (In prep.). Stress reduction and immune enhancement following psychological intervention for women with breast cancer. Repeated measures analyses reveal a significant intervention effect on the Impact of Events (IES) Scale. While both groups experienced a significant decline in stress with time, the decline for the intervention group was significantly greater. Repeated measures ANOVA's also reveal a significant intervention effect on T cell blastogenesis for both PHA and Con A assays. Moreover, the significant Group x Time interaction is evidenced across concentration levels for each assay. As seen in Fig. 4, PHA blastogenesis significantly increased for women in the intervention arm and decreased for women in the assessment only arm [$F(3, 155) = 6.25$, $p < .001$]; this interaction was found at all three dilutions, 2.5, 5, and 10. The same effect was found for ConA, [$F(1, 155) = 4.04$, $p < .05$; see Fig. 5], again across all three dilutions. Relevant data comes from Wiltschke et al. (1995). Using a prospective, longitudinal design, they followed 90 women with stages I - III breast cancer and reported that patients who showed an increase in PHA proliferation from initial to 12 months showed a significantly lower rate of relapse (2%) by 36 months than patients whose PHA proliferation declined during the same period (61%).

C. Quality Of Life and Health Behavior Outcomes

Andersen, B.L., Golden-Kreutz, D., Emery, C., Farrar, W., Carson, W., & Crespin, T. (In prep.). Psychological and behavioral benefits of psychological intervention for breast cancer patients. As indicated in Table 4, the groups did not differ significantly at the time of the initial assessment on quality of life. Analyses indicate a differential (i.e. Group x Time interaction) improvement for individuals in the intervention arm, in emotional distress, specifically anxious moods [POMS-Anx; $F(1, 176) = 6.09$, $p < .05$] (see Fig. 1). Another dimension of quality of life is social adjustment. Repeated measures analyses indicated a decline support from friends and family for women in the assessment only condition and stability of support for women in the intervention arm [Support from Friends and Family; $F(1, 132) = 3.69$, $p < .05$); see Fig. 2].

ANOVA's indicated that the intervention group changed dietary behaviors, and replaced high fat foods with low fat foods and significantly lowered overall fat intake [$F(1, 47) = 4.96$, $p < .05$]. Moreover, there is also evidence that negative health behaviors changed. In contrast to their equivalence at the initial assessment, analyses indicate lower smoking rates for the intervention arm compared to the assessment only arm at 4 months [$\chi 2 (1, 178) = 3.34$, $p < .05$] (see Fig. 3).

Figure 1 Stress: Anxiety Symptoms

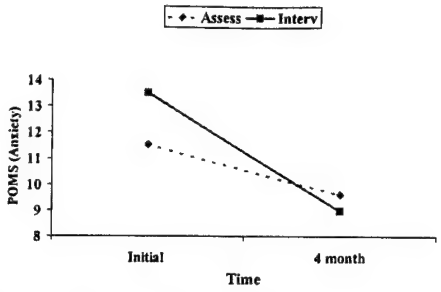


Figure 2 QoL: Social Adjustment

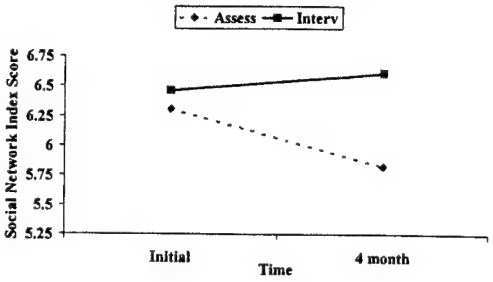


Figure 3 Health Behavior: Are You Smoking Now?

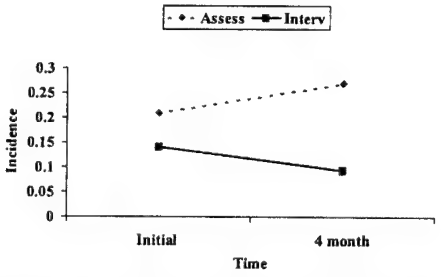


Figure 4 Immune: PHA (10:1)

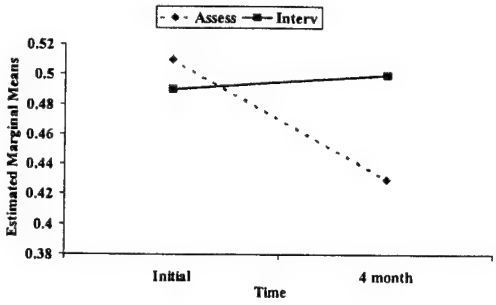
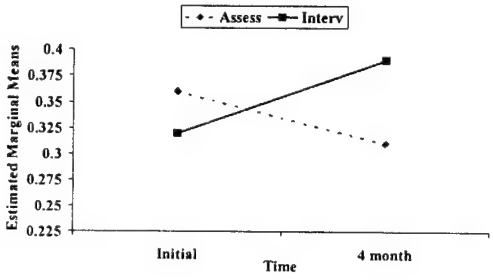


Figure 5 Immune: Con A (2.5)



D. Related topics

Golden-Kreutz, D.M., Browne, M., Frierson, G., & Andersen, B.L. (Under review). Statistical sense and sensibility: A psychometric analysis of the Perceived Stress Scale. "Stress" is an important construct in psychological literatures, particularly those focused upon health. The psychometric properties of a commonly used measure of global stress, the Perceived Stress Scale (PSS; Cohen, Kamarck, & Mermelstein, 1983), were examined. Data came from an important, stressful experience for a clinical sample--111 women recently diagnosed with breast cancer—which was assessed and then followed for two years. Exploratory Factor Analysis with oblique direct quartimin rotation revealed a two-factor solution, consisting of stress and counter-stress factors. Further hierarchical analyses revealed that the two factors comprised a second-order construct of perceived stress. Other validity (change across occasions and convergent/discriminent) and reliability (internal consistency and test retest) data are provided. Issues related to the wording/content of items and the use of hierarchical models for construct analysis are discussed.

6. KEY RESEARCH ACCOMPLISHMENTS

Methodologic

- Accrual goal of 200 was met and exceeded (N = 228, 114%).
- No notable biobehavioral or medical prognostic differences between acceptors and refusers.
- Retention rate (91%) is exceptional, significantly higher than the projected acceptable goal of 75% and impressive considering the stressful period of time for the women, the level of participation required, the multi-year commitment, and the rates of previous studies. Very high retention during years 2-5 of participation reflects positively on the patients' commitment to participation and the day-to-day management of this complex and labor intensive study.
- No differential attrition across groups.
- Research personnel have been shifted from accrual and intervention to data management and analysis.

Scientific

- With prospective data have documented the adverse effects of the cancer stressor for predicting both mental and physical health quality of life (Golden-Kreutz et al., under review; Golden-Kreutz, et al., under review; Yurek et al., 2000).
- Documented the adverse effects of the cancer stressor for immune responses (Andersen et al., 1998). Stress played a role in *functional* immune outcomes (e.g. NK cell lysis, blastogenesis), above and beyond disease predictors and/or transitory changes in cell numbers (e.g. NK cell count). This finding paved the way for the immune follow up studies.
- Data document that compliance with the psychological intervention is high and, further, the intervention produced important biobehavioral changes. (1) The intervention produced reductions in stress and concomitant increases in immunity. (2) The intervention produced quality of life improvements, including reductions in anxiety and increases in support from friends and family. (3) The intervention produced behavioral changes including reductions in cigarette intake among smokers and breast cancer relevant dietary changes, including reductions in fat intake.
- We have an unbiased and well described sample, and an intervention with which patients have been compliant and which produces therapeutic psychologic, behavioral, and biologic effects. Thus, the necessary conditions are in place to test for the contribution of biobehavioral factors to disease course.

7. REPORTABLE OUTCOMES (1996-2001)

Book

Baum, A., & Andersen, B.L. (Eds.) (2001). *Psychosocial interventions for cancer.* Washington D.C., American Psychological Association.

Manuscripts

Andersen, B.L. (1996). Psychological responses and sexual outcomes of gynecologic cancer. In J.J. Sciarra (Ed.), *Gynecology and Obstetrics* (Vol 4, chapter 68, pp. 1-18). Philadelphia: Harper & Row.

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(pp 241-244). Thousand Oaks: Sage.

Andersen, B.L., & Golden-Kreutz, D. (1998). Cancer. In A.S. Bellack & M. Hersen (Eds.), *Comprehensive clinical psychology*. Pergamon. (pp 217-236).

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Colloquia (Andersen)

Fox Chase Comprehensive Cancer Center and the College of Nursing, U. of Penn., Philadelphia, October 1966.
Parker Cancer Center and the Department of Behavioral Science, University of Kentucky, Lexington, Nov. 1996.
Cancer Center at Michigan State University, East Lansing, February 1997.
Wilford Hall Medical Center, Lackland Air Force Base, USAF, San Antonio, April 1997.
Carnegie Mellon University, Department of Psychology, Pittsburgh, September 1997.
Cancer Center at Indiana University, Indianapolis, February 1998.
Department of Preventive Medicine, School of Public Health, Ohio State, December 1999.
Comprehensive Cancer Center, The Ohio State University, January 2000.
Department of Obstetrics-Gynecology, The Ohio State University, January 2000.
Le Centre de Rescherche de L'Hotel-Dieu de Quebec, Universite Laval, Quebec, June 2000.
Department of Ob-Gyn, Baylor College of Medicine (Julian Wells Lecture), Dallas, June 2001.
Department of Psychiatry, Akron General Medical Center, Akron, July 2001.

Invited addresses/Plenary (Andersen)

Quality of life following cervix cancer. NIH Consensus Development Conference on Cervical Cancer, Bethesda, Md, April 1996.

Stress, immunity, and breast cancer: A biobehavioral intervention. Canadian Association of Psychosocial Oncology Annual Meeting, Montreal, Canada, May 1996. (Plenary).

Psychosocial interventions and cancer. American Psychological Association sponsored meeting at the University of Pittsburgh Cancer Institute. Program Chairs (A. Baum and B. Andersen), Pittsburgh, October 1997.

Psychoneuoimmunology. Local Biology Conference sponsored by the Social Science Research Council. Jekyll Island, GA, November 1997.

Biobehavioral model of cancer stress: Psychological, behavioral, and biological responses. Steven R. Heyman Memorial Lecture (Division 47). American Psychological Association Annual Meeting, Boston, August 1999.

Behavioral aspects of cancer in women. George Washington University Conference on Gender and Health in a Diverse Society. Washington, D.C., August 2000. (Plenary).

Biobehavioral outcomes in cancer. American Psychological Association Annual Meeting (Invited address, Division 38) Washington, D.C., August 2000.

Biobehavioral outcomes in cancer. European Health Psychology Society and the Division of Health Psychology of the British Psychological Society. St. Andrews, Scotland, September 2001. (Plenary).

Symposia

Testing the biobehavioral model of cancer stress and disease course. In A. Baum (Chair), Psychoneuroimmunology and cancer. International Congress of Behavioral Medicine, Washington D.C., March 1996.

Interventions for women with breast cancer. In N. Avis (Chair), Psychosocial adjustment and quality of life among breast cancer survivors. American Psychological Association Meeting on Psychosocial and Behavioral Factors in Women's Health: Psychosocial and Behavioral Factors in Women's Health: Research, Prevention, Treatment, and Service Delivery in Clinical and Community Settings, Washington, D.C., September 1996.

Biobehavioral models of cancer stress and disease course. In H. Tomes (Chair, Organizer for the Public Interest Directorate, American Psychological Association), Behavioral and social science contributions to other health sciences. American Association for the Advancement of Science, Seattle, February 1997.

Psychological interventions for women with cancer. In J.Kiecolt-Glaser (Chair), Psychoneuroimmunology. Women's Health Research Conference, Washington D.C., June 1997.

Sexual self concept and adjustment following cancer. In E.M. Palace (Chair), Women's sexual health. International Academy of Sex Research, Baton Rouge, LA., July 1997.

Biobehavioral models of cancer stress and disease course: An update. In M. Andrykowski (Chair), Psychological interventions for cancer patients. American Psychological Association Annual Meeting, Chicago, August 1997.

Stress, immunity and breast cancer. In C. Johansen (Chair), Stressors and stress reduction interventions in cancer

patients: Effects on adjustment, health and immunity. International Congress of Behavioral Medicine, Copenhagen, Denmark, August 1998.

Biobehavioral aspects of cancer recurrence. In M.A. Andrykowski and A. Baum (Chairs), Presidential Miniconvention on Cancer--State of the art research programs in cancer. American Psychological Association Annual Meeting, Boston, August 1999.

Convention Presentations/Posters

Cyranowski, J.C., & Andersen, B. L. (1996, March). Women's sexual self views and their relation to sexual behaviors, responses and affects. Congress of International Society of Behavioral Medicine, Washington, D.C.

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Golden-Kreutz, D., Andersen, B., Yurek, D., Collier, A., Chaput, N., Cox, N., Lester, J., & Farrar, W. (1996, March). Stress and Immunity Breast Cancer Project: Psychological and behavioral outcomes. Congress of International Society of Behavioral Medicine, Washington, D.C.

Cyranowski, J.C., & Andersen, B. L. (1996, July). Women's sexual schemas: A cognitive approach to women's sexuality. Society for the Scientific Study of Sexuality, Pittsburgh.

Cyranowski, J.C., & Andersen, B. L. (1996, August). Women's sexual self schemas: Empirical support for a bivariate model. American Psychological Association Convention, Toronto.

Andersen, B.L., Golden-Kreutz, D., Farrar, W., Glaser, R., & Sheridan, J. (1996, September). The benefits of psychological/behavioral interventions for women with breast cancer. American Psychological Association Interdisciplinary Conference on Psychosocial and Behavioral Factors in Women's Health, Washington, D.C.

Aarestad, S.L., Yurek, D.L., & Andersen, B.L. (1997, April). Sexual self-schema and sexual morbidity among gynecologic and breast cancer survivors. Society of Behavioral Medicine, San Francisco.

Nielsen-Gammon, E., Farrar, W.B., & Andersen, B.L. (1997, April). Traumatic stress symptomatology, distress, and coping in women with breast cancer. Society of Behavioral Medicine Meeting, San Francisco.

Golden-Kreutz, D., Yurek, D., & Andersen, B.L. (1997, August). Psychosocial interventions: Improving sexual functioning of women with breast cancer. Meeting of the American Psychological Association , Chicago.

Golden-Kreutz, D., Farrar, W., Courtney, M.E., Armstrong, R., & Andersen, B.L. (1997, August). Recruitment and retention: Conducting clinical research with breast cancer patients. Meeting of the American Psychological Association, Chicago.

Golden-Kreutz, D., & Andersen, B.L. (1997, November). Older adults in longitudinal clinical trials: Issues of recruitment and retention. Gerontological Society of America, Cincinnati.

Andersen, B., Farrar, W., & Glaser, R. (1997, November). Stress alters immune responses following surgical treatment for regional breast cancer: Studies from the Stress and Immunity Breast Cancer Project. The Department of Defense Breast Cancer Research Program Meeting, Washington, D.C.

Andersen, B.L., Golden-Kreutz, D., & Farrar, W. (1997, November). Stress reduction and enhanced coping from a psychological/behavioral intervention for women with regional breast cancer: Studies from the Stress and Immunity Breast Cancer Project. The Department of Defense Breast Cancer Research Program Meeting,

Washington, D.C.

Yurek, D., Frierson, G., DiLillo, V., & Andersen, B. (1998, April). Individual difference and sexual adjustment following breast cancer. Society of Behavioral Medicine, New Orleans Louisiana.

Golden-Kreutz, D., DiLillo, V., Farrar, W., & Andersen, B. (1998, July). Benefits of cognitive/behavioral interventions for women with breast cancer. World Congress of Behavioral and Cognitive Therapies, Acapulco, Mexico.

Golden-Kreutz, D., Courtney, M., DiLillo, V., & Andersen, B. (2000, April). Objective stressors vs. subjective stress and their relationship to depressive symptoms: Examining the psychological responses to breast cancer diagnosis and treatment. Meeting of the Society of Behavioral Medicine, Nashville.

Frierson, G., Golden-Kreutz, D., Browne, M., & Andersen, B. (2000, April). The construct independence of perceived stress and depressive symptoms. Society of Behavioral Medicine, Nashville.

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Andersen, B.L. (2001, September). Sexual self schema and adjustment following cancer. European Health Psychology Society and the Division of Health Psychology of the British Psychological Society. St. Andrews, Scotland.

Patents and licenses applied for and/or issued: NA

Academic degrees/training that are supported by this award:

Postdoctoral students

Deanna Golden-Kreutz, Ph.D., 1996-1999
Sharla Wells, Ph.D., 1999-present

Dissertation:

Susan Aarestad, Ph.D. (2000)
Georitia Frierson, in progress

MA/MS thesis:

Kristin Carpenter, in progress
Georita Frierson, M.A., 2000
Larissa Demshuk, M.S.W., 2000
Heather Lawrence, in progress
Rebecca Shelby, in progress
Lisa Thornton, in progress

Development of cell lines, tissue or serum repositories: NA

Informatics such as data bases and animal models, etc.: NA

Funding applied for based on work supported by this award:

Walther Cancer Institute; 8/97-8/01. B. Andersen (PI): Biobehavioral aspects of cancer recurrence. Total costs: $120,000.

Dana Foundation; 1/1/00-12/31/01. B. Andersen (co-PI) and W. Carson (co-PI): Mechanisms of stress-related effects on host immune responses in breast cancer. Total direct costs: $100,000.

Employment or research opportunities applied for and or received on experiences/training supported by this award:

American Cancer Society; 1/1/01-12/31/03. S. Wells (PI) and B. L. Andersen (Mentor): Social support and health outcomes of partners of recurrent breast cancer patients. Total costs are $138,000.

National Institutes of Health/NCI; Grant No. 1 RO1 CA92704; 7/1/01-6/30/06. B. Andersen (PI): Psychological intervention for women with breast cancer. Total costs: $4,048,478.

8. CONCLUSIONS

To summarize, we view stress, QoL, health behaviors, and compliance as the major factors in a conceptual model of adjustment to the cancer stressor. Also part of the model are the physiological systems--the endocrine and immune systems--which may be important ones for moderating the effects of stress on disease processes. This experimental test of the model is a "simple" experimental design--a comparison of treatment vs. no treatment. This was a strategic next step for the field as it provides cause--effect data for the presence of an intervention producing enhanced psychological and behavioral outcomes, immune responses, and health effects. In addition to the biobehavioral model, the specific design of the intervention, with intensive and maintenance phases, is novel.

Important findings have already emerged from the research. We have documented that the psychological stress of cancer diagnosis and breast cancer surgery produces important psychological and immune effects. The stress is instrumental in increasing a woman's risk for experiencing depressive symptoms (Golden Kreutz et al., under review), body image and sexual distress (Yurek, Farrar, & Andersen, in press), and subsequent declines in mental health and physical aspects of quality of life. Stress is also instrumental in producing a broad band down regulation of womens' immune responses (Andersen et al., 1998). We found NK cell function and T cell proliferation and blastogenesis is impaired.

We now have data to document impressive biobehavioral--psychological, behavioral, and immune effects--of the intervention. We found that women receiving the intervention showed 1) lower stress and fewer anxiety symptoms symptoms, 2) improved social support, 3) enhanced immunity as indexed by T cell blastogenesis responses, in contrast to the responses of the patients in the Assessment only study arm. In sum, these data show a convergence of psychological, behavioral, and immune effects with a psychological/behavioral intervention.

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Journal of Consulting and Clinical Psychology
2000, Vol. 68, No. 4, 697-709

0022-006X/00/$5.00 DOI: 10.1037//0022-006X.68.4.697

Breast Cancer Surgery: Comparing Surgical Groups and Determining Individual Differences in Postoperative Sexuality and Body Change Stress

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Women diagnosed and surgically treated for regional breast cancer (N = 190) were studied to determine the sexual and body change sequelae for women receiving modified radical mastectomy (MRM) with breast reconstruction in comparison with the sequelae for women receiving breast-conserving therapy (BCT) or MRM without breast reconstruction. The sexuality pattern for women receiving reconstructive surgery was one that was significantly different—with lower rates of activity and fewer signs of sexual responsiveness—than that for women in either of the other groups. Significantly higher levels of traumatic stress and situational distress regarding the breast changes were reported by the women receiving an MRM in contrast to the women treated with BCT. Using a model to predict sexual morbidity, regression analyses revealed that individual differences in sexual self-schema were related to both sexual and body change stress outcomes.

More than 180,000 women are diagnosed with breast cancer each year, and it is estimated that 1 in 9 will develop the disease by age 85 (American Cancer Society [ACS], 2000). Surgery is usually the initial treatment for invasive breast cancer. Surgical options include breast-conserving therapy (BCT; often called *lumpectomy*) and axillary node dissection or a modified radical mastectomy (MRM), which includes removal of all breast tissue as well as the axillary lymph nodes. Not all women receiving an MRM are eligible for breast reconstruction (i.e., tissue expander with a permanent implant, autologous tissue transfer, or a permanent implant), but those who are may elect to receive it at the time of mastectomy. Still, other women may elect to have a bilateral mastectomy (removal of the breast with the tumor as well as removal of the other, disease-free, breast). Even though this is rare, women who request such extended surgery are typically those women with a strong familial history (i.e., a first-degree relative, a mother, died of the disease at a young age), who are young when diagnosed (e.g., <45 years old), and who actively want to reduce their risk of recurrence, as the remaining breast is the most common site for disease progression (Harris, Morrow, & Bonadonna, 1993).

Clinical psychologists juxtapose these medical facts about breast cancer with concern about the psychological and behavioral sequelae of the disease. Since the earliest research on the psychological aspects of cancer, breast cancer surgery has been viewed as difficult and, in some sense, traumatic. Although cancer, per se, can be a devastating illness, disease in the breast was regarded as an especially difficult insult (e.g., Bard & Sutherland, 1955; Renneker & Cutler, 1952). Implicit was the notion that a woman (and perhaps her sexual partner) would see herself as a "changed" sexual person following mastectomy. For example, in 1980 Derogatis offered a framework for two primary and "integrally related" (p. 2) components of sexual self-identity—sexuality and body image—as being directly affected by diagnosis and treatment

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The Stress and Immunity Breast Cancer Project is an ongoing study conducted at the Department of Psychology and the James Cancer Hospital and Research Institute, Ohio State University. The study was supported by a grant from the American Cancer Society (PBR-89), the Longaberger Company–American Cancer Society Grant for Breast Cancer Research (PBR-89A), U.S. Army Medical Research Acquisition Activity Grants (DAMD17-94-J-4165 and DAMD17-96-1-6294), and a grant from the National Institute of Mental Health (1 RO1 MH51487). This research was also supported in part by a grant from the General Clinical Research Center (MO1-RR0034); the Ohio State University Comprehensive Cancer Center Core Grant from the National Cancer Institute (P30 CA16058); and the Department of Psychology and the College of Social and Behavioral Sciences, Ohio State University.

These data were in partial fulfillment of the dissertation requirements for Debora Yurek.

We thank the study participants for their time and assistance. In addition, we acknowledge the following individuals for their contributions: research/graduate assistants Susan Aarestad, Elizabeth Street Bromet, Nicole Chaput, Angela Collier, Larisa Demshuk, Melissa Douglas, Sarah Grimes, Katheryn Pingel, Jessica Walker, and Laura Wielonski and nurses Beth Putz and Jan Varga-Spangler for conducting the psychological/nursing assessments; surgical oncologists William Burak, William Carson, Julian Kim, Gregory LaValle, Deborah Martinez, Michael Walker, and Lisa Yee and medical oncologists Kelly Cawley, Chris Rhoades, Arthur Sagone, Victoria Seewalt, Michael Stanek, and James Ungerleider for accrual; Mary Elizabeth Courtney for data management and Deanna Golden-Kreutz, Vicki DiLillo, and Laura Peterson for project management; Georita Frierson for statistical assistance; and Jill Cyranowski, Steven Beck, Mark Elliot, Charles Emery, and Robert McCallum for helpful comments on an earlier version of this article.

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of breast cancer. Contemporary reviews highlight the importance of sexuality for cancer survivors. As Gotay and Muraoka (1998) noted, "the aspects of QoL [quality of life] that pose the most difficulty for survivors are likely to vary by cancer site, but this literature strongly implies that sexual functioning and/or satisfaction is a common issue for many survivors, regardless of diagnosis or treatment" (p. 664).

Conclusions such as the latter are familiar (e.g., Andersen, 1985), even though the methodologies for this research have been, at times, modest. Specifically, sexuality and body image constructs have been ill defined and operationalized and difficult to assess as separate constructs (e.g., questionnaire items such as "I feel sexually attractive" are viewed as assessing both domains). Even so, a meta-analysis of psychosocial outcomes of breast cancer surgery separated the constructs and reported consistent psychologic advantages for lumpectomy (i.e., breast-conserving surgery) in contrast to mastectomy for body image and, to a lesser but still significant extent, for marital/sexual adjustment (Moyer, 1997). In fact, Moyer (1997) concluded that "the largest and most robust effect size, showing benefits for breast conserving surgery for body/self-image, is already a firmly established finding" (p. 290).

For those women who receive mastectomy, by choice or necessity, reconstructive surgery may be included. Because some types of reconstruction at the time of mastectomy may add additional cost and surgical morbidity (i.e., slower wound healing, extra days in hospital, and added blood loss as well as anesthesia), research is needed to determine the benefit added. A certain motivation of reconstruction is for "better" quality of life outcomes than with MRM alone. Thus, the first goal of the present research was to examine the postoperative sexual and body image sequelae for women receiving MRM with immediate reconstruction (MRMw/R). Their responses were compared with the differential responses of the most studied surgical groups—women receiving either BCT or MRM only.

Related to this goal was our strategy to examine a broader conceptualization of the emotional distress and potential trauma surrounding breast changes. We included three convergent yet nonoverlapping domains for assessment. First, the previous decades of research had included a measure of "body image." Although body image can be conceptualized in many ways, it is body satisfaction that has been frequently examined (e.g., Muth & Cash, 1997); thus, a standard measure of body satisfaction (Berscheid, Walster, & Bohrnstedt, 1973) was included. Second, women receiving more extensive breast surgery report situational distress when their body is (or potentially might be) exposed; this distress may be greatest when a woman is with a sexual partner but may also occur when she is alone (e.g., standing and dressing in front of a mirror; Beckmann, Johansen, & Blichert-Toft, 1983; Kemeny, Wellisch, & Schain, 1988; Margolis, Goodman, & Rubin, 1990; Noguchi et al., 1993). Thus, we generated examples of situational stressors for the content of items. Third, intrusive thinking and avoidance are two important dimensions of the subjective stress response to traumatic stressors, and individuals who report involuntary, distress-related ruminations following traumatic life events are also those who suffer the greatest negative effects. This is true for war veterans or rape victims (Keane & Wolfe, 1990; Roszell, McFall, & Malas, 1991), as well as breast cancer patients when they are assessed regarding their intrusive thoughts of cancer treatment or their avoidance of reminders of their disease (Cordova et al., 1995). Thus, we assessed traumatic stress—intrusive thoughts and avoidant behaviors—related to the breast changes. The three domains—traumatic stress, situational distress, and body satisfaction—were used to assess differential levels and opposing valences (i.e., positive body satisfaction vs. negative subjective stress) of reactions to the body changes brought with the three types of breast cancer surgery (BCT, MRMw/R, and MRM).

In addition to describing the disease and/or treatment factors correlated with sexual and body image outcomes, our research has tested theoretical models for the prediction of psychological/behavioral morbidity (e.g., Andersen, 1994; Andersen, Woods, & Copeland, 1997) and disease course (Andersen, Kiecolt-Glaser, & Glaser, 1994; Andersen et al., 1998). This research step is important for progress in quality of life research and for identification of women in greatest need for psychosocial care, and it is a step facilitated by the prior decades of psychological research (see Meyerowitz, 1980, as an example of an early review). It is also timely, as nearly 50% of women diagnosed with breast cancer will survive at least 15 years (ACS, 2000) and will, necessarily, "adjust" to surgical sequelae. Moreover, there is a current controversy surrounding the medical management of women identified to be at increased risk for the disease (Eisen & Weber, 1999) and the large numbers of women diagnosed with noninvasive breast tumors ("Stat Bite," 1998). Some of the latter women receive aggressive surgical management. For example, Hartmann et al. (1999) studied women with a well-defined family history of breast cancer who underwent a prophylactic bilateral mastectomy; their report, suggesting a reduction of at least 90% in both the incidence of breast cancer and risk of death from the disease, may well increase the frequency of women choosing such extensive surgical solutions to manage their risk for and fears about breast cancer.

For the prediction of psychological and behavioral morbidity surrounding sexual functioning, our model has included known correlates of sexuality for women (e.g., demographic factors, such as age; behavioral factors, such as previous frequency of sexual intercourse; and psychological factors, such as level of sexual satisfaction) and health/illness variables (e.g., menopausal status and extent of disease and treatment; Andersen, 1994), but these variables do not fully account for who does and who does not experience significant sexual morbidity (e.g., Andersen, Anderson, & deProsse, 1989a). Individual differences appear to be important as well.

The construct of sexual self-concept or sexual self-schema has been proposed (Andersen & Cyranowski, 1994; Andersen, Cyranowski, & Espindle, 1999) and tested (Andersen et al., 1997) as an important individual difference variable for sexual domains. Sexual self-schema is a novel, cognitive view about sexual aspects of oneself. It functions not only as a quick referent of one's sexual history but also as a point of origin for information—judgments, decisions, inferences, predictions, and behaviors—about the current and future sexual self. It regulates intrapersonal sexual processes, but sexual schema also appears to mediate the interpersonal aspects of sexual relationships. Those who differ in the valence of their sexual self-views have very different sexual lives. Women with a positive sexual schema, for example, enter sexual relationships more willingly, have a more extensive behavioral repertoire, evidence more positive emotions when in sexual relationships, and anticipate having positive sexual relationships in the future. Also, the affects and behaviors indicative of loving, intimate attachments are central to women with a positive sexual schema (Cyranowski & Andersen, 1998). In contrast, women with a negative sexual

schema tend to describe themselves as emotionally cold or unromantic; further, they are behaviorally inhibited in their sexual and romantic relationships. They may describe themselves as self-conscious, embarrassed, or inexperienced in sexual matters. Importantly, our longitudinal data indicate that these are stable self-views, impervious, for example, to the passage of time or the waxing and waning of specific sexual or romantic relationships.

Thus, the second goal of this study was to test the contribution of sexual schema to women's postoperative sexual and body change outcomes. The test of the schema construct is framed within a conceptual model for predicting psychological and behavioral morbidity, which controls for important, prior history variables (e.g., prior frequency of intercourse and menopausal status) and disease/treatment factors (Andersen, 1994). We hypothesized that individual differences in sexual self-schema can function as a diathesis, and they can be important in predicting sexual morbidity and/or dysfunction following the onset of a sexually relevant stressor (see Cyranowski, Aarestad, & Andersen, 1999, for a complete discussion). Support for this general hypothesis was found with gynecologic cancer survivors (N = 61; Andersen et al., 1997). When comparisons were made with an age-matched sample of women without cancer, the expected disruption in sexuality was found for the women with cancer, due in part to the effects of their radical surgery and/or radiotherapy to the pelvis and genitals (e.g., Andersen et al., 1989a). More relevant, however, was the finding that sexual self-schema was a significant predictor of both posttreatment sexual behavior and responsiveness for the cancer survivors in analyses that controlled for precancer levels of sexual behavior or responsiveness, extent of disease/treatment, and menopausal symptoms.

To enhance the clarity of the comparison of the surgery groups and rigor of the test of sexual schema, we obtained a homogeneous breast cancer sample and conducted the assessment at a single, critical period. Women with regional malignant disease were selected as these women have a similar prognosis and adjuvant treatment trajectory. The timing of the assessment was controlled to reduce variability and, simultaneously, maximize the acute emotional distress accompanying the breast changes. That is, all of the women were assessed in the early postsurgery/preadjuvant therapy period. These are the days when, for example, the chest wound has healed, women are visited by Reach to Recovery volunteers, and prostheses, if needed, are selected and first worn. This is, indeed, an early, critical period for women diagnosed with breast cancer (Rollin, 1976).

Method

Participants

Participants were 190 women who had been diagnosed and surgically treated for Stage II (87%) or Stage III (13%) breast cancer. The staging schema of the American Joint Committee on Cancer and the International Union Against Cancer was used, and the obtained distribution corresponds to national trends for women with regional breast disease (ACS, 2000). Women were, on average, 36 days postsurgery (SD = 16 days, range = 5–101 days), and they had not yet begun their adjuvant therapy. The distribution of surgery type was as follows: 78 (41%) women received lumpectomy (BCT), 29 (15%) women received MRMw/R, 79 (42%) women received MRM, and 4 (2%) women received elective bilateral mastectomy. Women were anticipating the start of their adjuvant therapy (e.g., combinations of hormonal therapy [Tamoxifen], radiotherapy, chemotherapy, and/or chemotherapy followed by bone marrow transplantation) in the days following their accrual and assessment.

A demographic analysis revealed that the mean age for the participants was 51 years (SD = 11 years, range = 30–84 years), the mean level of education was 15 years (some college), the annual personal income ranged from $2,000 to $200,000, annual family income ranged from $5,000 to $350,000, and 67% of the sample was employed outside the home. The racial distribution of the group was as follows: 169 (89%) were Caucasian, 19 (10%) were African American, and 2 (1%) were Hispanic.

Marital/partner status of the sample was 65% married (M = 22 years), but 72% were living with a partner. Nine percent of the women had never been married, and 28% of the women were living alone. Of the partnered relationships, it appeared that all but 3 (2 lesbian and 1 bisexual) were heterosexual. The sexually active status of each woman at cancer diagnosis was determined. A woman was defined as previously "sexually active" if she reported the occurrence of intercourse (or an equivalent intimate activity) at least once a month for the 2 months immediately preceding her diagnosis. Thus, 65% of the women were sexually active prior to diagnosis, and at the time of the assessment, 58% of them had resumed intercourse (or an equivalent form of intimacy) since surgery.

Measures

Individual Differences

The Sexual Self Schema Scale for Women (Andersen & Cyranowski, 1994) was used. This scale contains 26 trait adjectives (e.g., *cautious, loving, open-minded,* and *experienced*) plus 24 adjective fillers (e.g., *generous, shallow, kind,* and *practical*) that are self-rated from 0 (*not at all descriptive of me*) to 6 (*very descriptive of me*). Factor analytic studies have shown that the items tap three dimensions: (a) Passionate/Romantic, (b) Open/Direct, and (c) Embarrassed/Conservative. Items from Factors 1 and 2 are summed, and items from Factor 3 are subtracted so that a total schema score can range from −42 to 102, with numerically lower scores representing a negative sexual self-view and higher scores reflecting a more positive sexual self-view. Factor/factor correlations are .47 for Factor 1/Factor 2, −.03 for Factor 1/Factor 3, and −.13 for Factor 1/Factor 3; internal consistency for the scale is .70. For this sample, the mean total schema score was 59 (SD = 13.31, range = 14–89), which is comparable with that previously reported for healthy women (i.e., M = 60, SD = 14.15; Andersen & Cyranowski, 1994). Test–retest reliability indicates stability, with 2-week estimates of .89, 2-month reliability of .88, and an 18-month reliability of .72. The measure predicts a wide range of sexual attitudes, behaviors, and responses (Cyranowski & Andersen, 1998) and cognitions (Cyranowski & Andersen, in press). Also, it is uncontaminated with social desirability or negative affect biases, and process studies indicate that respondents are unaware that a sexual construct is being assessed (see Andersen & Cyranowski, 1994, for a complete discussion).

Sexuality

Sexual behavior. Two types of data were obtained. Past sexual behavior was assessed for the 2 months prior to diagnosis for the frequency of intercourse and the frequency of kissing. Each was rated using a 10-point rating scale (0 = *this activity did not occur,* 5 = *three times per week,* 9 = *this activity occurred more than 4 times a day*). The two items were summed. Data from female cancer and healthy samples indicate a 4-month test–retest reliability of .75 for such ratings (Andersen & Broffitt, 1988) and an ability of these items to distinguish cancer and healthy groups (e.g., Andersen et al., 1997).

Current sexual behaviors, including behaviors evidencing sexual approach as well as avoidance, were assessed with a 10-point scale (0 = *this activity did not occur,* 5 = *three times per week,* 9 = *this activity occurred more than 4 times a day*). Approach behaviors included affectionate kissing of partner, passionate ("deep") kissing of partner, erotic embrace, and kissing of sensitive (nongenital) areas and were drawn from a factor

analytic study (Andersen & Broffitt, 1988) of the Sexual Experience Scale (Derogatis & Melisaratos, 1979). A current sexual behavior score was obtained by summing the four items; internal consistency was .84. The total score ranged from 0 to 36. Women also rated the frequency of their sexually avoidant behaviors (e.g., frequency of declining, refusing, or avoiding intercourse) since their breast surgery, and their avoidance score ranged from 0 to 7.

Sexual response cycle. A 27-item questionnaire assessing the psychophysiologic phases of the sexual response cycle was used. Items were drawn from a structured interview format (Andersen et al., 1989a), but when used as a questionnaire the items had distinguished the responses of women with cancer versus healthy women (Andersen et al., 1997; Cyranowski & Andersen, 1998). Items for each phase of the response cycle—desire, excitement, orgasm, and resolution—were included along with general satisfaction items. Women rated the frequency of the response/feelings on a 5-point scale ranging from 0 (*never*) to 4 (*always*). A principal axis factor analysis, with an oblique (Harris Kaiser) rotation, revealed three sexual response cycle factors—Sexual Desire (6 items), Sexual Arousal (7 items), and Orgasm/Resolution (10 items)—with an additional factor for General Satisfaction (4 items). Items assessing Sexual Desire focused on sexual interest (e.g., "How often were you not interested in your partner's suggestions for sex?" and "How often did you desire sex?"), ratings of Sexual Arousal included physiologic markers (e.g., awareness of vaginal lubrication, feelings that the vagina was "too tight" for penetration, and pain or discomfort), and Orgasm/Resolution was assessed with indicators of climax (e.g., awareness of throbbing sensations in the vagina, feelings of body warmth, sweating, heavy breathing, and rapid breathing) and the feelings of general relaxation, contentment, and tension release. Finally, 4 items assessed General Satisfaction with sexuality (e.g., satisfaction with the frequency of sexual activity).

Negative valence items were reverse-scored prior to summing the items for a scale. Scores could range from 0 to 108 for total responsiveness (sum of all of the items), 0 to 24 for Sexual Desire, 0 to 28 for Sexual Arousal, 0 to 40 for Orgasm/Resolution, and 0 to 16 for General Satisfaction. Internal consistency estimates for total responsiveness was .91, and those for each scale were .77 (Sexual Desire), .80 (Sexual Arousal), .86 (Orgasm/Resolution), and .72 (General Satisfaction). Sexual response cycle factor intercorrelations ranged from .35 to .64, and the sexual response cycle correlations with the General Satisfaction factor ranged from .48 to .66. For this sample, the mean scores were 70.7 (range = 28–98) for total responsiveness, 12.9 for Sexual Desire (range = 0–21), 18.6 for Sexual Arousal (range = 2–27), 28.1 for Orgasm/Resolution (range = 4–39), and 10.4 for General Satisfaction (range = 4–16).

Global evaluation. A 9-point scale ranging from 0 (*could not be worse*) to 8 (*could not be better*; Derogatis & Melisaratos, 1979) was used for women to rate their view of their sexual life prior to their cancer diagnosis. This global evaluation is sensitive to pre–post cancer treatment effects (e.g., Andersen et al., 1989a, 1997) and cancer groups (Andersen & Jochimsen, 1985). The median was 4.0, the mean was 4.2, and the standard deviation was 1.9.

Body Change Stress

Traumatic stress. Research investigating psychological reactions to stressful life events has identified responses of intrusion and avoidance as characterizing individuals' subjective experience to the stressor. Intrusion has been typically operationalized as involuntary thoughts or images associated with the traumatic stressor, repetitive behaviors, or strong waves of distress-laden feelings (Allen, 1994), whereas avoidance responses have included measurement of behavioral inhibition related to the meanings and/or consequences of the event and emotional blunting (Keane & Wolfe, 1990).

For our purpose, change in physique due to breast cancer surgery was hypothesized as the traumatic life event. Thus, the 15-item Breast Impact of Treatment Scale (BITS) was developed to examine intrusive thoughts (nine items) and avoidant reactions (six items) associated with breast changes. Patterned after the Impact of Events Scale (IES; Horowitz, Wilner, & Alvarez, 1979), the BITS item content was derived from prior breast cancer research assessing posttreatment concerns of women receiving breast surgery (e.g., avoidance of nudity, thoughts of disfigurement, and feelings of body self-consciousness; Beckmann et al., 1983; Carver et al., 1994; Meyer & Aspegren, 1989; Pozo et al., 1992; Schain et al., 1983), but the items were worded to tap intrusive (e.g., "How my body has changed pops into my mind" and "When I see other women, I think that my body appears different than theirs") and avoidant processes (e.g., "I don't want to deal with how my body looks" and "I avoid looking at or touching my scar").

The internal structure of the BITS was examined using exploratory factor analysis (CEFA software; Browne, Cudeck, Tateneni, & Mels, 1998). Based on prior research on traumatic stress, two factors (Avoidance and Intrusion) were estimated by ordinary least squares (OLS) and an oblique rotation to a partially specified target (Browne, 1972) was conducted. Analyses indicated that all but one of the residuals for the OLS matrix were under .05 and the largest absolute residual was .20. These two results indicated that the data matrix and the hypothesized model were highly correlated. This factor solution was supported by several fit measures (root-mean-square error of approximation [RMSEA] = .067, 90% confidence interval = .046–.087, p = .08; Browne & Cudeck, 1993). It should be noted that a nontraditional p value above .05 and an RMSEA between .05 and .08 indicate support for the model (Browne et al., 1998).

The first factor was labeled *Intrusion* and included eight items; the second factor, labeled *Avoidance*, included the remaining seven items. Internal consistency was .88 for the Intrusion factor and .84 for the Avoidance factor; the factors correlated .70. Consistent with the scoring of the IES (Horowitz et al., 1979), response choices were weighted (0 = *not at all*, 1 = *rarely*, 3 = *sometimes*, 5 = *often*) for the three degrees of positive endorsement of frequency. Items were summed to obtain subscale scores corresponding to Factor 1/Intrusion (range = 0–45) and Factor 2/Avoidance (range = 0–30), and the BITS total score (range = 0–75) was calculated by summing the factor subscales. We found that the scale is uncontaminated by social desirability, as correlation with the Marlowe–Crowne Social Desirability Scale (Crowne & Marlowe, 1960) was −.09. These data lend support to the internal validity of the BITS. For this sample, the mean value for the total score was 25.9 (range = 0–67), the mean value for the Avoidance subscale was 10.6 (range = 0–33), and the mean value for the Intrusion subscale was 15.3 (range = 0–38).

Situational discomfort. Five situations typically reported as distressing to women following surgical treatment for breast cancer were generated. The content included looking at the chest while undressed, disrobing in front of a sexual partner, a sexual partner viewing the surgical site, undressing in the presence of other women, and allowing others (e.g., female friends) to see the surgical site. Items such as these have differentiated women receiving alternative surgeries (see, e.g., Bartelink, van Dam, & van Dongen, 1985; Beckmann et al., 1983; Kemeny et al., 1988; Margolis et al., 1990; Meyer & Aspegren, 1989; Noguchi et al., 1993). A 5-point rating of distress (e.g., 0 = *not at all distressed*, 4 = *extremely distressed*) was used, and items were summed for a total distress score (range = 0–20). Internal consistency was .86. The mean score among women in this sample was 6.3 (SD = 4.9, range = 0–20).

Body satisfaction. The 10-item version (short form) of the Body Satisfaction Scale (BSS; Andersen & LeGrand, 1991; Berscheid et al., 1973) was used to assess satisfaction with the physical body (i.e., body parts) following surgical treatment. Factor analysis has yielded two factors: Satisfaction With Appearance (including facial and sexual parts [shape and size of breast/s and genitals]) and Weight or Body Correlates of Weight (hips, thighs, and buttocks; Andersen & LeGrand, 1991). In addition, a single item assessed satisfaction with overall appearance. Participants rated the 10 body items on a 6-point satisfaction/dissatisfaction scale (1 = *extremely satisfied*, 3 = *satisfied*, 6 = *extremely dissatisfied*), with a higher score indicating greater body dissatisfaction. Internal consistency was .84.

Table 1
Adjusted Mean Scores for Four Surgical Groups for Measures of Sexuality and Body Change Stress and ANCOVA and Multiple Comparison Results for Three Surgical Groups

Area and outcome	Surgical group				p
	BCT	MRMw/R	MRM	BiM	
Sexual behavior					
Current	18.06_a	12.71_b	16.57_a	16.67	.05
Avoidance of activity	0.91	0.81	1.32		
Resume intercourse (%)	87_a	57_b	68_b	33	.05
Sexual response cycle	76.29_a	63.83_b	70.64		.05
Desire (absence of)	13.03	12.14	12.85		
Arousal	20.60_a	17.85	16.39_b		.05
Orgasm/resolution	30.56_a	24.46_b	29.62_a		.01
General satisfaction	11.34_a	9.02_b	10.86_a		.05
Body change stress					
Traumatic stress	17.86_a	32.71_b	31.36_b	37.67	.001
Avoidance	7.95_a	13.12_b	12.00_b	18.33	.001
Intrusion	10.28_a	19.56_b	19.02_b	19.33	.001
Situational distress	3.29_a	8.60_b	8.63_b	10.50	.001
Body satisfaction	33.38_a	32.28_a	36.39_b	32.00	.05

Note. For the outcomes, a higher score indicates a greater level of behavior/response, with the exception of body satisfaction, for which a higher score indicates greater body dissatisfaction. Within rows, different subscripts indicate significant differences ($p < .05$) for the multiple comparison tests comparing the BCT, MRMw/R, and MRM groups. Empty cells indicate insufficient data. ANCOVA = analysis of covariance; BCT = breast conservation therapy; MRMw/R = modified radical mastectomy with reconstruction; MRM = modified radical mastectomy; BiM = bilateral mastectomy.

A BSS total score was obtained by summing all of the items; the mean total score was 34.42 (SD = 7.96, range = 10–58).

Procedures

Recruited consecutively from mid-1994 through mid-1999, the majority of the women (81%) were being treated at a National Cancer Institute–designated, university-affiliated Comprehensive Center and the remainder (19%) were receiving treatment at community hospitals within a 90-mi (144-Km) radius of the Cancer Center. All of the study participants were enrolled in a larger parent study, the Stress and Immunity Breast Cancer Project,[1] a randomized clinical trial.

Only women meeting the above disease stage and treatment schedule were eligible. Some women meeting the criteria were excluded from participation for any of the following reasons: age less than 20 years or greater than 90 years, any previous cancer diagnosis, having begun adjuvant therapy, severe mental retardation, severe psychopathology (e.g., schizophrenia or noncompliance with bipolar disorder treatment), dementia, or other life-threatening conditions (e.g., renal failure). Participation rates fluctuated over the course of the study depending on hospital factors (e.g., influx of new surgeons into the department and relocation of the breast oncology outpatient clinic) but averaged 75%. Of those approached for participation, the major (top three) reasons women gave for nonparticipation were insufficient time (29%), too far of a distance (e.g., >40 mi [>64 Km] from study hospital) to travel for participation (32%), and not interested (27%). Analyses of participants and refusers revealed no significant differences on sociodemographic (i.e., age, marital status, and race) or disease/treatment-relevant (i.e., menopausal status, estrogen receptor, stage, number of positive nodes, and days since surgery) variables.

All of the participants came to the General Clinical Research Center at the university or a regional outpatient breast cancer clinic of the Cancer Center, where psychologic, behavioral, and medical data were collected and a 60-ml blood sample was taken. The majority of the data for the present investigation were administered along with the questionnaire battery and structured interview as part of their initial assessment for the Stress and Immunity Breast Cancer Project when accrual began; approximately 4 months into accrual, the sexuality and body change stress assessment was expanded (i.e., the sexual response cycle measure and the impact of treatment measure were added) to complete the assessment. Participants were unaware of this addition to the assessment battery. Women were paid $30 for participation and reimbursed for their parking/transportation expenses (approximately $4). Following this initial assessment, women were randomized for the larger study and then followed for future assessments.

Results

Preliminary Analyses

Descriptive analyses indicated that 4 women had received elective bilateral mastectomy. Because of the small numbers in this group, they were eliminated from all of the analyses of covariance (ANCOVAs) and regression analyses, resulting in a sample size of 186. However, in the interest of providing clinical detail, we display their data in Table 1 along with the data from the three-group comparisons.

Comparisons were made between the remaining surgical groups (BCT, MRMw/R, and MRM) on variables that could potentially covary with outcome. There were no significant differences ($p > .10$) between the groups on days since surgery or the sociodemographic variables of education, marital status, or race, although the groups differed significantly ($p < .001$) in age (BCT = 50 years, MRMw/R = 45 years, and MRM = 54 years). Data have suggested that younger women may report greater affective distress

[1] Data from the first 116 women accrued to the Stress and Immunity Breast Cancer Project (including 116 of the 190 women included here) have been published (Andersen et al., 1998). The latter article documented a negative relationship between stress and immunity; there is no overlap of measures between Andersen et al. and the present report.

following breast cancer surgery (Ganz et al., 1993), and generational differences in sexual behavior have been reported (Lauman, Gagnon, Michael, & Michaels, 1994). Therefore, age was used as a covariate in all of the subsequent analyses.

Data for women who were not sexually active prior to surgery (i.e., denied having engaged in a sexually intimate activity, such as intercourse, at least once in the 2 months prior to surgery) were included only for the body change analyses. Considering all reasons, we found that 35% of the sample indicated that they were not sexually active prior to their diagnosis. The most common reason for sexual inactivity was the lack of an intimate partner (92%).

Analyses for the sexuality data were conducted using only the data from the 122 women reporting prior sexual activity, and thus the sample sizes were as follows: $n = 53$ for BCT, $n = 25$ for MRMw/R, and $n = 44$ for MRM. For this sample, there were no significant differences ($ps > .05$) between the sexually active women in the surgical groups on days since surgery or the sociodemographic variables of education, marital status, or race, but the groups differed significantly ($p < .05$) in age (BCT = 48 years, MRMw/R = 45 years, and MRM = 51 years). Again, age was used as a covariate in the analyses for sexual outcomes.

Part 1: Comparison of Surgical Groups: MRMw/R Versus BCT or MRM

Sexual Behavior

The assumption of the group design used here was that at an earlier point in time, prior to the diagnosis of cancer, the three surgical groups had comparable levels of sexual functioning and did not differ on dimensions that might covary with postsurgical sexual outcome. To test these assumptions, we conducted a one-way ANCOVA design (using age as the covariate) on the women's reports of the frequency of intercourse, frequency of kissing, and global evaluation of their sexual life for the 2 months prior to their cancer diagnosis. No significant group differences ($ps > .10$) were found. Grand means were as follows: intercourse frequency = 3.14 (3 = *once per week*), kissing frequency = 6.90 (7 = *once per day*), and global evaluation = 4.71 (4 = *average*, 5 = *above average*). These data indicate that the sexually active women in the three surgical groups reported statistically equivalent levels of sexual behavior and satisfaction for the months immediately prior to their cancer diagnosis, suggesting that the groups had comparable levels of prior sexual functioning.

Analyses for approach and avoidance of sexual behaviors/activities were conducted. ANCOVAs for the measure of the frequency of current sexual activities were significant, $F(2, 101) = 4.23$, $p < .05$, and the least significant difference test was used for follow-up pairwise multiple comparisons (see Table 1 for mean scores across groups and multiple comparison results). They indicated that the frequency of current sexual behavior was significantly lower for the women receiving reconstruction (for MRMw/R, $M = 12.71$) than the frequency of behavior of women who received either lumpectomy (BCT; $M = 18.06$) or MRM ($M = 16.57$). However, the ANCOVA was not significant for the frequency of avoidant sexual activity. We also tested whether there was a differential rate of resumption of sexual intercourse following breast cancer surgery. The Pearson chi-square was significant, $\chi^2(2, N = 107) = 8.69$, $p < .05$, and the rates of resuming intercourse for the groups are presented in Table 1. They indicate that more of the women receiving BCT (87%) resumed intercourse than did women receiving mastectomy (57% and 68% for the MRMw/R and MRM groups, respectively).

For the sexual response cycle data, we first conducted an ANCOVA on the total score before proceeding with analyses for the subscales. The ANCOVA for the total scale was significant, $F(2, 55) = 3.40$, $p < .05$. Follow-up ANCOVAs were then conducted for each subscale composing the total score. The ANCOVA for the desire phase was not significant, although ANCOVAs for all of the remaining phases and general satisfaction were significant: for Sexual Arousal, $F(2, 57) = 3.34$, $p < .05$; for Orgasm/Resolution, $F(2, 63) = 5.62$, $p < .01$; and for General Satisfaction, $F(2, 65) = 4.37$, $p < .05$. Multiple comparisons indicated that women treated with BCT reported significantly greater arousal during sexual activity than did women treated with MRM. For both Orgasm/Resolution and General Satisfaction, follow-up multiple comparisons indicated that the women receiving BCT and MRM reported significantly more signs and symptoms of orgasm and feelings of sexual satisfaction during their current sexual activity than did women receiving MRMw/R (see Table 1 for means).

Body Change Stress

Three aspects of body change were assessed: traumatic stress; situational distress; and, in contrast, self-reports of body satisfaction. An ANCOVA (age as the covariate) was first conducted on the full scale score for the measure of traumatic stress and was significant, $F(2, 148) = 19.62$, $p < .0001$. Therefore, follow-up ANCOVAs for the Intrusion, $F(2, 153) = 20.20$, $p < .0001$, and Avoidance, $F(2, 149) = 9.83$, $p < .001$, subscales were conducted and were also found to be significant. Multiple comparison analyses for the total score and the two subscales all yielded the same pattern of results (see Table 1 for means). That is, the lowest levels of traumatic stress, manifested by intrusive thoughts and avoidant behaviors regarding breast changes, were reported by the women receiving BCT, whereas women receiving mastectomy, with reconstruction (MRMw/R) or without (MRM), reported significantly higher levels of traumatic stress. In fact, the scores for the mastectomy groups were more than 1 *SD* above the mean of the scores for the BCT group.

The ANCOVA for the measure of situational distress was also significant, $F(2, 135) = 29.15$, $p < .0001$. Follow-up multiple comparisons (see Table 1) indicated that women receiving BCT reported significantly less situational distress than did women receiving MRM or MRMw/R.

The ANCOVA for the full scale score of the body satisfaction measure was also significant, $F(2, 176) = 3.76$, $p < .05$. Follow-up multiple comparisons (see Table 1) indicated that the lowest level of body satisfaction was reported by the women receiving MRM only.

Part 2: Tests of the Relationship Between Sexual Self-Schema and Sexual Morbidity and Body Change Stress

The above analyses indicate that women with breast cancer who received radical surgery, with or without reconstruction, experienced significantly greater sexual disruption and body change stress than did women who received more conservative surgical therapy (i.e., BCT), consistent with hypotheses concerning impor-

Table 2
Hierarchical Regression Analyses Testing Model of Morbidity (Andersen, 1994) and Sexual Self-Schema in Relationship to Sexual Behavior Outcomes

Step	Predictor	β	R	R^2	t	df
	Predicted outcome: Current sexual activity					
1	Menopausal status	−0.21	.24	.06	−2.50**	104
2	Prior frequency of intercourse	0.32	.45	.20	3.69***	103
3	Stage of disease	−0.01	.45	.20	−0.06	102
4	Extent of treatment[a]	0.35	.54	.29	3.13**	100
		0.27			2.36*	
5	Sexual self-schema	0.18	.57	.32	2.08*	99
	Predicted outcome: Avoidance of sexual activity					
1	Menopausal status	−0.13	.12	.01	−1.35	106
2	Prior frequency of intercourse	0.06	.12	.01	0.58	105
3	Stage of disease	0.03	.13	.02	0.31	104
4	Extent of treatment[a]	0.06	.16	.03	0.44	102
		0.15			1.12	
5	Sexual self-schema	−0.24	.29	.08	−2.44*	101

[a] There are two levels of this variable (see Footnote 2).
* $p < .05$. ** $p < .01$. *** $p < .001$.

tance of the extent of disease/treatment for psychosocial outcomes (e.g., Andersen, 1994). The second goal of the research was to test the added contribution of a psychological individual difference variable, sexual self-schema, when evaluating sexual morbidity and body change stress. We conducted preliminary one-way analyses of variance (ANOVAs; group [BCT vs. MRMw/R vs. MRM]) and compared the surgical groups on the schema scores. Analyses for the total score as well as the three subscales were not significant (all $ps > .05$), indicating that sexual self-schema did not covary with surgery group.

Variables were entered in regression analyses in the order hypothesized for the prediction of posttreatment sexual morbidity (i.e., Andersen, 1994; see, e.g., Andersen et al., 1997). For the sexuality analyses, we entered the following variables: menopausal status (i.e., pre- vs. postmenopausal; this variable is relevant to genital sexual responses [e.g., Walling, Andersen, & Johnson, 1990] and, indirectly, serves as a proxy for age); sexual functioning prior to diagnosis (i.e., operationalized with the previous frequency of intercourse); stage of disease (i.e., Stage II vs. Stage III); extent of treatment (i.e., surgery type)[2]; and, finally, sexual self-schema. For the body change analyses, the following variables were entered: menopausal status; stage of disease; extent of treatment; and, finally, sexual self-schema. For the sexuality analyses, only data from women who were sexually active prior to their diagnosis were used; data from the entire sample were used for the body change analyses.

Sexuality

We conducted two hierarchical multiple regression analyses to evaluate current sexual behaviors, both approach and avoidant sexual activity. Both analyses produced comparable, significant findings, and the results are provided in Table 2. As would be hypothesized from sexuality and cancer literatures, in the prediction of frequency of current sexual activity (approach), the menopause and prior frequency of intercourse control variables added significant incremental variance. The extent of surgery variable was also significant. Specifically, significant partial coefficients for both lumpectomy and mastectomy variables indicated that there were significant differences in current sexual activity means between women receiving reconstruction (MRMw/R) and both BCT and MRM women after controlling for all other predictors in the equation. Following these, schema added an additional significant 3% of the variance, for a total of 32% of the variance accounted for by the predictors. In the analysis for avoidance of sexual activity, only the sexual self-schema variable was a significant predictor, adding 5%, for a total of 8% of the variance accounted for by all of the predictors.

We conducted regression analyses for the total score on the sexual response cycle measure (see Table 3). Here, the extent of surgery accounted for significant portion of variance (13%). Significant partial coefficients for both lumpectomy and mastectomy variables indicated that there were significant differences in total sexual responsiveness means between MRMw/R women and both BCT and MRM women after controlling for all other predictors in the equation. Finally, sexual schema added an additional 12% of the variance, for a total of 31% of the variance accounted for by the predictors. Follow-up regression analyses were conducted for the subscales for the response cycle measure, and the data are displayed in Table 3. In each case, the analyses were significant, and sexual self-schema accounted for significant additional variance.

[2] For the purpose of the regression analyses, the extent of treatment (i.e., surgery type) variable was recoded into two dummy variables containing all of the information of the three-level categorical variable. The first dummy variable was coded 1 for BCT and 0 for the other groups; the second dummy variable was coded 1 for MRM group and 0 for the other groups. In addition to determining the amount of variance surgery group accounts for in the outcome variables, significance tests for regression coefficients for the BCT and MRM dummy variables provide for the testing of specific hypotheses about differences in outcome variable means between the BCT group and the MRM group and between the MRM group and the MRMw/R group.

Table 3
Hierarchical Regression Analyses Testing Model of Morbidity (Andersen, 1994) and Sexual Self-Schema in Relationship to Sexual Response Cycle Outcomes

Step	Predictor	β	R	R^2	t	df
	Predicted outcome: Total sexual responsiveness					
1	Menopausal status	−0.16	.17	.03	−1.39	58
2	Prior frequency of intercourse	0.04	.20	.04	0.30	57
3	Stage of disease	−0.13	.24	.06	−1.06	56
4	Extent of treatment[a]	0.39	.44	.19	2.52*	54
		0.31			1.95*	
5	Sexual self-schema	0.36	.56	.31	3.01***	53
	Predicted outcome: Sexual desire					
1	Menopausal status	−0.27	.27	.07	−2.56**	76
2	Prior frequency of intercourse	0.18	.37	.14	1.65	75
3	Stage of disease	−0.01	.37	.14	−0.09	74
4	Extent of treatment[a]	0.07	.40	.16	0.51	72
		0.15			1.05	
5	Sexual self-schema	0.34	.52	.27	3.19**	71
	Predicted outcome: Sexual arousal					
1	Menopausal status	−0.32	.35	.13	−3.47**	60
2	Prior frequency of intercourse	0.05	.37	.14	1.52	59
3	Stage of disease	−0.09	.39	.15	−0.76	58
4	Extent of treatment[a]	0.20	.45	.21	1.59	56
		0.01			0.03	
5	Sexual self-schema	0.11	.52	.27	2.27*	55
	Predicted outcome: Orgasm/resolution					
1	Menopausal status	−0.10	.08	.01	−0.86	66
2	Prior frequency of intercourse	0.00	.09	.01	−0.03	65
3	Stage of disease	−0.11	.14	.02	−0.98	64
4	Extent of treatment[a]	0.51	.46	.21	3.38***	62
		0.46			3.02**	
5	Sexual self-schema	0.23	.51	.26	2.01*	61

[a] There are two levels of this variable (see Footnote 2).
* $p < .05$. ** $p < .01$. *** $p < .001$.

Schema accounted for 11% of the variance in the total of 27% for Sexual Desire, 6% of the variance in the total of 27% for Sexual Arousal, and 5% of the variance in the total of 26% for Orgasm/Resolution.

Body Change Stress

All of the participants were included in regression analyses investigating traumatic stress, situational distress, and body satisfaction. The regression analysis with the total score on traumatic stress measure was significant, as were the follow-up regression analyses for the Intrusion and Avoidance subscales. As the pattern of findings across the scales was similar, we provide for illustration in Table 4 the results for the total score. Of the control variables, only the extent of surgery added significant incremental variance (21%). Significant partial coefficients for the BCT variable indicated significant mean differences in traumatic stress for MRMw/R and BCT women after controlling for all of the other predictors in the equation. Sexual self-schema added an additional 3%, for a total of 24% of the variance in traumatic stress accounted for by the predictors. Examining the subscales, we found that sexual self-schema accounted for an additional significant 6% of the variance in the total of 18% for the Avoidance score and 2% of the variance in the total of 25% for the Intrusion score.

The regression analysis for the prediction of the situational distress was also significant, and results are displayed in Table 4. Of the control variables, the extent of surgery was most influential, accounting for a significant 30% of the variance. Significant partial coefficients for the BCT variable indicated significant mean differences in situational discomfort for MRMw/R and BCT women after controlling for all of the other predictors in the equation; the t test for the MRM coefficients was not significant. Sexual self-schema accounted for an additional significant 3%, for a total of 35% of the variance in situational distress scores.

Finally, the regression analysis for the body satisfaction measure was not significant. In combination, the control and schema variables accounted only for 5% of the variance in the prediction of body satisfaction scores.

Follow-Up Analyses

We conducted post hoc analyses examining the significant sexual self-schema findings. We view sexual self-schema as a construct, underscoring that "the measure is more than the sum of the

Table 4
Results of Hierarchical Regression Analyses Testing Model of Morbidity (Andersen, 1994) and Sexual Self-Schema in Predicting Body Change Stress Outcomes

Step	Predictor	β	R	R^2	t	df
		Predicted outcome: Traumatic stress				
1	Menopausal status	−0.00	.01	.00	−0.03	152
2	Stage of disease	−0.08	.01	.00	−1.08	151
3	Extent of treatment[a]	−0.51	.46	.21	−4.75***	149
		−0.08			−0.71	
4	Sexual self-schema	−0.16	.49	.24	−2.24*	148
		Predicted outcome: Situational distress				
1	Menopausal status	0.06	.10	.01	0.88	139
2	Stage of disease	−0.02	.13	.02	−0.22	138
3	Extent of surgery[a]	−0.60	.57	.32	−5.81***	136
		−0.08			−0.73	
4	Sexual self-schema	−0.17	.59	.35	−2.42*	135

[a] There are two levels of this variable (see Footnote 2).
* $p < .05$. *** $p < .001$.

parts" (Andersen & Cyranowski, 1994, p. 1094). Our view is best operationalized by the total score calculation (see description in the Method section). However, some individuals may have interest in the contribution of the individual factor scores in the prediction of outcomes. For this reason, we provide in Table 5 the semipartial correlations with the major outcome variables for the three factor subscales of the schema scale. The variables controlled in these partials are those included in the steps of the regression analyses (i.e., menopausal status, prior frequency of intercourse, state of disease, and extent of treatment) provided in Tables 3 and 4. We did not control for the other two sexual self-schema factors when an individual factor was entered on the final step.

These data indicate that for many sexual and body change stress outcomes, only the schema scale total score itself predicted outcomes. That is, for arousal, orgasm/resolution, traumatic stress, and the specific aspects of traumatic stress that included intrusive thoughts, none of the individual factors predicted outcomes. For other outcomes, individual factor scores were influential (i.e., Factor 1 [current sexual activity], Factor 2 [total score for sexual response cycle and lack of sexual desire], and Factor 3 [avoidance of sexual activity, lack of sexual desire, situational discomfort, and avoidance aspects of traumatic stress]), although no one factor was predominant.

Discussion

In recent decades, considerable discussion and change has taken place in oncology regarding the appropriate standard surgical therapy for women with breast cancer. Surgery has shifted from radical mastectomy, to MRM, to breast-conserving surgery (lumpectomy) followed with radiotherapy. An impetus for clinical trials comparing the surgical therapies was to reduce morbidity (defined broadly, but including quality of life) without sacrificing cure rate. Currently, the data suggest that conservative surgery

Table 5
Unique Variance Accounted for by the Factor Scores of the Sexual Self Schema Scale for Women (Andersen & Cyranowski, 1994) in Predicting Sexual Behavior, Sexual Response Cycle, and Body Change Stress Outcomes

	Sexual self-schema factors		
Predicted outcome	Factor 1: Passionate/Romantic	Factor 2: Open/Direct	Factor 3: Embarrassed/Conservative
Current sexual activity	.052*	.003	.008
Avoidance of sexual activity	.009	.033	.074*
Sexual response cycle	.050	.060*	.053
Desire	.022	.046*	.120**
Arousal	.018	.024	.048
Orgasm/resolution	.018	.024	.008
Traumatic stress	.001	.003	.023
Avoidance	.001	.011	.040*
Intrusion	.001	.001	.013
Situational distress	.006	.014	.021*

Note. Data are squared semipartial correlations.
* $p < .05$. ** $p < .01$.

(i.e., BCT) with radiotherapy produces comparable survival rates with that achieved with MRM for women with early stage disease (National Institutes of Health Consensus Conference, 1991). However, not all women are eligible for BCT because of the size/spread or location of the tumor and must receive mastectomy; still, others, when given the choice, elect mastectomy. Subsequently, women are faced with the question of reconstruction: proceed or not, and if so, when? The circumstance of having options or choices regarding cancer treatment is the exception. When it does occur, psychological and behavioral data can be critically important, as individuals are attempting to make the best choices to preserve, maintain, or, possibly, enhance their future quality of life. Thus, these data provide an important perspective on this period of acute distress—the days and weeks immediately following breast cancer surgery.

The first goal of the research was to examine the postoperative sexual and body change sequelae for women receiving MRMw/R in comparison with women receiving either BCT or MRM. Considering the sexual outcomes, the data suggest that the sexuality pattern for women receiving reconstructive surgery (MRMw/R) was one that was significantly different—with lower rates of activity and fewer signs of sexual responsiveness—than that for women receiving BCT and oftentimes lower than that for women receiving MRM without reconstruction. The behavioral disruption was particularly evident, as the level of current sexual activity for the women receiving reconstruction was more than 1 *SD* below the means of the other groups; also, over 40% of the women had not yet resumed intercourse in the month intervening from surgery to the assessment. This represents a noticeable behavioral change, as women reported that prior to their diagnosis they had intercourse, on average, of once per week. For the BCT and MRM groups, the finding of statistical equivalence between the groups for many of the sexual outcomes (e.g., current activity, orgasm/resolution, and satisfaction) is consistent with the meta-analysis findings of Moyer (1997); she reported extremely small (and nonsignificant) effect size (ES) differences between BCT and MRM groups, considering both randomized ($ES = 0.06$, *ns*) and nonrandomized ($ES = 0.11$, *ns*) investigations.

Comparison of the three groups on dimensions of body change stress reveals a consistent pattern of results for the three surgical groups, but one differing from the sexual outcomes previously discussed. Specifically, significantly higher levels of traumatic stress and situational distress regarding the breast changes were reported by all of the women treated with mastectomy (i.e., both MRM and MRMw/R) in contrast to the women treated with breast conservation (BCT). The pattern of less body change stress for women receiving BCT versus MRM is not surprising. Indeed, this is a robust effect, found in both randomized and nonrandomized investigations, regardless of whether the follow-up interval is short or long (i.e., less than or greater than 12 months following surgery; Moyer, 1997). Many fewer studies have included a sample of women who have received reconstruction. The finding of equivalent levels of distress for both the MRMw/R and MRM groups, however, is consistent with data from cross-sectional studies of heterogeneous samples of women assessed from 2 months to 2 years (Mock, 1993; Noguchi et al., 1993) following surgery, as well as for longer than 3 years since surgery (Margolis et al., 1990; Wellisch et al., 1989). Also, the data from the single study that randomized women to either BCT or MRMw/R (Schain, d'Angelo, Dunn, Lichter, & Pierce, 1994) found better outcomes for the women randomized to BCT and no apparent body image benefit for the women receiving reconstruction.

In summary, the first goal of the research—to characterize the outcomes for women receiving breast reconstruction (MRMw/R)—found that their immediate postsurgery sexual behavior and sexual responses are disrupted, and significantly more so than women receiving lesser surgery (BCT) or comparable breast surgery but no reconstruction (MRM). Moreover, the data suggest that the reconstruction achieves no reduction in body change stress, at least when assessed during the early postsurgery period, as the reconstruction group reported levels of stress equivalent to those of the women receiving MRM only and both mastectomy groups reported body change stress significantly higher (in some cases twice as high) as the responses of the women receiving BCT. We also provided descriptive data on the few women who requested bilateral mastectomy. Even though additional numbers of women are necessary to document the reliability of these estimates, the values are consistent with the hypothesis that more radical surgical therapy does, indeed, result in greater psychological and behavioral morbidity. These women report significant situational distress and avoidant behaviors (e.g., avoiding looking at her chest and turning away from her sexual partner).

The second goal of the research was to test the contribution of a psychological variable—sexual self-schema—to sexual and body change outcomes. Our intent was to make this a difficult test, as we were aware of the powerful role that prior levels of sexual behavior have in predicting sexual activity, as well as the important role that cancer treatments can have in affecting quality of life. Indeed, the latter factors are regarded as so important that individual differences are rarely considered, even in the case of Phase III cancer clinical trials (i.e., randomized trials comparing treatments thought to differ in efficacy), which are believed to produce, a priori, differential quality of life outcomes (e.g., Moinpour et al., 1998). In the regression analyses for both sexuality and body change stress, sexual self-schema consistently added significant incremental variance beyond that explained by the control variables, many of which were important contributors, as hypothesized. Thus, it would appear that women with more negative sexual self-views are more apt to engage in lower levels of sexual activity, have difficulties with their sexual responsiveness, and be vulnerable to heightened body change stress. The common characteristics of negative schema women—lower sexual arousability and greater sexual embarrassment and negativity—are likely contributors to make them vulnerable to coping poorly with the breast changes and disruption of sexual intercourse brought on with the cancer stress, hospitalization, and recovery. Moreover, this psychological difference among women plays an important role even when other powerful factors—such as the extent of the surgery—are considered.

The importance of sexual schema found here replicates our initial test of sexual self-schema predicting sexual outcomes for gynecologic cancer survivors (Andersen, Woods, & Copeland, 1997). The data are consistent with the construct conceptualization of the measure, and it is our recommendation that the total score of the measure be used. Even when individual factor scores are influential (in contrast to the total score) in the prediction of outcomes, their content and direction of effects are consistent with the psychometric strategies used in the construction of the scale and the provision of validity data for the measure (e.g., Andersen & Cyranowski, 1994; Cyranowski & Andersen, 1998). For exam-

ple, we have noted that "Factor 3 has a general inhibitory effect on behavior as well as positive sexual affect" (Andersen & Cyranowski, 1994, p. 1084). This is consistent with our findings that Factor 3 predicts avoidance of sexual activity and lack of sexual desire.

Considering the clinical utility of these results, one future use of the schema measure might be to test it as a screening measure in a model for the prediction of sexual morbidity (Andersen, 1994) to identify women at greatest risk for quality of life disruption in the domains of sexuality or body change following breast surgery. Indeed, in an era of shrinking resources for health care services of all types, preventive efforts that target psychosocial care to those in greatest need are important. For example, these data suggest that postmenopausal women receiving MRM (with or without reconstruction), and those with more negative sexual self-schemas, are at heightened risk for sexual disruption and body change stress. Importantly, clinical psychologists have several effective strategies to reduce sexual and body-related anxieties (see, e.g., Wincze & Carey, 1991) that have applicability to female cancer survivors and their partners (see also Andersen & Elliot, 1993).

This study offered a novel conceptualization of the emotional distress—and perhaps trauma—surrounding breast changes. As we noted, women's reports of distress due to a changed "body image" (however defined) have been long-standing and robust, despite nebulous measurement strategies. Even though we found group differences here, measures of "satisfaction" with body parts have been inconsistent in their ability to document change following cancer treatments (e.g., Andersen & LeGrand, 1991; Langer, Prohaska, Schreiner-Frech, Ringler, & Kubista, 1991), suggesting that "satisfaction–dissatisfaction" scales or ratings of body parts may not be the most appropriate measurement strategies or conceptualization for the concerns of women undergoing significant breast changes. Indeed, women's endorsements of avoidance behaviors and intrusive thoughts would suggest that the stress of this experience can at least mimic (if not be identical to) the psychological remnants of a traumatic stressor. As with many traumatic stressors, the occurrence of uncontrollable events (e.g., intrusive thoughts "popping into awareness") likely heighten the levels of women's general distress as well. Still, there may be important phenomenological differences between the traumatic body change stress of breast cancer and the psychological trauma of other stressors (e.g., rape or war). For example, the body change stressor for women treated for breast cancer remains (i.e., the chest is permanently changed) and other less tangible aspects (e.g., the fear of recurrence and death) remains to be faced each day. For now, the strategy of conceptualizing breast changes as a precipitant to significant stress-related responses (i.e., behavioral avoidance and intrusive thoughts) appears to produce useful data. In addition, this conceptualization and measurement strategy suggests directions for choosing psychological interventions (e.g., anxiety-reduction techniques for avoidant behaviors and cognitive–behavioral strategies for problematic thoughts) to treat women with clinical levels of body change stress.

Finally, we note particular methodologic aspects of this study. The sample was predominantly Caucasian, and so generalizability of the findings to other ethnic groups may be limited. The large, homogeneous sample and control of the timing of the assessment at a critical period were important design features, as we were able to differentiate psychological and behavioral sequelae for the three surgeries and test for individual differences in outcomes. Although an important strength was control over the timing of the assessment (i.e., the data document the sexual and body change stress in the early surgical recovery period), continued follow-up data are necessary to document the reliability of these changes for later follow-up. However, our longitudinal data with gynecologic cancer patients indicated that to the extent that sexual problems develop early in the recovery period, the majority of them do not resolve during the following year, and, in addition, some women who resume intercourse still develop sexual problems at a later time (Andersen, Anderson, & deProsse, 1989b). However, we will need to follow the present sample to determine if this is their scenario, too, or if their sexual activity returns to former levels and their body change stress declines.

To some, the difficult outcomes for the women receiving reconstruction may be surprising. However, consideration of the technical and clinical aspects of reconstruction may be informative (see Brown, 1991, for a more complete discussion of patient concerns). For example, reconstruction with an implant produces a breast "mound" without a breast nipple. Also, breast implants do not have the same tactile sensation, as the implanted breast can feel "hard" compared with one's other breast. These, and related experiences, are the outcomes to which women undergoing reconstruction were adjusting at the time of our assessment. However, as a woman becomes more familiar with these qualities of the breast, there may be some reduction in stress. In addition, women with reconstruction do, indeed, experience what many report as the main benefits of reconstruction—greater ease in clothing style and convenience—and the escape from wearing a prosthesis. Whether or not these or other benefits occur and are of sufficient importance to allow women who underwent reconstruction to become less avoidant, more sexually responsive, and less vulnerable to intrusive, stressful thoughts remains to be discovered. What is clear, however, is that women at risk for such difficulties can be identified at the time of surgery, and effective sexual and cognitive–behavioral therapies exist to prevent or minimize the types of or magnitude of psychosocial and quality of life disruptions shown here. To the extent that clinical psychologists and other behavioral scientists can provide data to forecast quality of life outcomes, they will have provided a mechanism and pathway to prevent stress from the breast cancer experience.

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Received February 4, 1999
Revision received November 23, 1999
Accepted December 6, 1999 ■

REPORTS

Stress and Immune Responses After Surgical Treatment for Regional Breast Cancer

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Background: **Adults who undergo chronic stress, such as the diagnosis and surgical treatment of breast cancer, often experience adjustment difficulties and important biologic effects. This stress can affect the immune system, possibly reducing the ability of individuals with cancer to resist disease progression and metastatic spread. We examined whether stress influences cellular immune responses in patients following breast cancer diagnosis and surgery.** ***Methods:*** **We studied 116 patients recently treated surgically for invasive breast cancer. Before beginning their adjuvant therapy, all subjects completed a validated questionnaire assessing the stress of being cancer patients. A 60-mL blood sample taken from each patient was subjected to a panel of natural killer (NK) cell and T-lymphocyte assays. We then developed multiple regression models to test the contribution of psychologic stress in predicting immune function. All regression equations controlled for variables that might exert short- or long-term effects on these responses, and we also ruled out other potentially confounding variables.** ***Results:*** **We found, reproducibly between and within assays, the following: 1) Stress level significantly predicted lower NK cell lysis, 2) stress level significantly predicted diminished response of NK cells to recombinant interferon gamma, and 3) stress level significantly predicted decreased proliferative response of peripheral blood lymphocytes to plant lectins and to a monoclonal antibody directed against the T-cell receptor.** ***Conclusions:*** **The data show that the physiologic effects of stress inhibit cellular immune responses that are relevant to cancer prognosis, including NK cell toxicity and T-cell responses. Additional, longitudinal studies are needed to determine the duration of these effects, their health consequences, and their biologic and/or behavioral mechanisms. [J Natl Cancer Inst 1998; 90:30–6]**

A diagnosis of cancer and cancer treatments are objective, negative events in an individual's life. Although negative events do not always produce stress and a lowered quality of life, data from many studies document severe, acute stress at cancer diagnosis *(1)* and during recovery *(2)*. The negative psychologic responses of individuals with cancer to the diagnosis and treatment are important in their own right because these responses are targets for cancer control efforts *(3,4)*. In addition, data suggest that stress responses are accompanied by nonrandom (i.e., correlated) negative changes in a broad range of immune responses. This study examines from a biobehavioral perspective whether stress influences cellular immunity in women with breast cancer after diagnosis of breast cancer and during the postsurgical period *(5)*.

Meta-analyses *(6,7)* suggest that psychologic stress and the experience of life stressors are reliably associated with negative immune alterations in noncancer subjects; i.e., "higher" levels of stress (e.g., self-reports of stress or negative affects, such as sadness or clinical diagnoses of depression) are related quantitatively and functionally to "reduced" cellular immune responses, such as lowered natural killer (NK) cell lysis. This effect has been found regularly for individuals in the midst of chronic stressors, and some of the largest responses and changes have been found for lengthy stressors and those that have interpersonal components.

Illustrative data come from Kiecolt-Glaser, Glaser, and colleagues *(8–11)*, who have followed individuals during the long, stressful experience of giving care to a spouse diagnosed with Alzheimer's disease. Not surprisingly, caregivers report high levels of distress and negative affect as they cope with their relative's difficult behavior and mental deterioration *(8)*. Moreover, these researchers have found, for example, that NK cells obtained from caregivers are less responsive to the cytokine recombinant interferon gamma (rIFN γ) and recombinant interleukin 2 (rIL-2) than are cells obtained from matched community control subjects *(9)*. In addition, these highly stressed subjects have a poorer proliferative response to mitogens *(8)*, exhibit substantial deficits in the antibody and virus-specific T-cell responses to an influenza virus vaccine *(10)*, and demonstrate stress-related defects in wound repair *(11)*.

There are fewer data on the relationship between stress and immunity among cancer patients. Levy et al. *(12)* reported on these relationships in 66 women with stage I or II breast cancer 3 months after treatment (lumpectomy or mastectomy with or without adjuvant therapy). In ad-

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See "Notes" following "References."

dition to finding that estrogen receptor status predicted NK cell lysis, these researchers found that social support—a variable hypothesized to *reduce* stress—contributed significantly to a regression model predicting *higher* NK cell activity. These findings suggest that how a person responds to stress may also influence how stress, in turn, influences the immune response.

There is considerable evidence that patients with cancer express abnormal cellular immune responses; these abnormal responses have been found in patients with many different types of cancer *(13–15)*, including breast cancer *(16,17)*. Stressors are not generic, and they would not be expected to have identical physiologic outcomes. So too, the immune response involves a cascade of responses and events that can occur over time. For these reasons, we used a homogeneous breast cancer subject sample and timing of assessment to test the relationship between stress and several components of the cellular immune response, including NK cell and T-cell functions.

Women who had been diagnosed with breast cancer and who had undergone surgery for the breast cancer were studied before they began adjuvant therapy. Since we were interested in the contribution of stress in predicting an immune response above and beyond known correlates, we controlled for naturally occurring factors in our statistical analyses that affect the immune responses—specifically, age, disease stage (lymph node status), and recovery (days since surgery) *(18)*. Because the immune system contains a considerable amount of redundancy, we focused on three components that would each provide important, but complementary, information.

First, we measured NK cell lysis. We chose to measure NK cell lysis because those cells are believed to act early in the immune response and they have been demonstrated to play an important role in immune surveillance against tumors and virally infected cells *(19–21)*. Second, we measured the ability of the NK cells to respond to rIFN γ and rIL-2. It has been shown that lymphokine-activated killer (LAK) cells are highly cytotoxic against a wider variety of tumor cells than those lysed by resting NK cells *(22)*, an effect also observed in patients with breast cancer *(23)*. Finally, to obtain information on the T-cell response, we measured the response of peripheral blood leukocytes (PBLs) to two mitogens—phytohemagglutinin (PHA) and concanavalin A (Con A)—and we induced proliferation by stimulating the T cells with a monoclonal antibody (MAb) to the T-cell receptor.

Subjects and Methods

Patient Eligibility and Data Collection

Participants were 116 women who had been diagnosed with invasive breast cancer and who were surgically treated within the last 4 months but who had not yet begun adjuvant treatment. Women were from 14 to 101 days (mean = 37 days; median = 33 days) after surgery for stage II (70%) or III (30%) invasive breast cancer. We used the American Joint Committee on Cancer and the International Union Against Cancer staging system. The women ranged in age from 31 to 84 years (mean = 52 years). Recruited consecutively from mid-1994 to early 1997, the majority (82%) were being treated at a National Cancer Institute-designated, university-affiliated Comprehensive Cancer Center, and the remainder (18%) were receiving treatment at local community hospitals. All women came to the General Clinical Research Center at the university where psychologic, behavioral, and medical data were collected and a 60-mL blood sample was taken from them. Assessments were conducted between 8:00 AM and 12:00 AM to reduce diurnal variability.

Stress Measure

The Impact of Event Scale (IES) *(24)* is a standardized self-report questionnaire used to examine intrusive thoughts ("I had dreams about being a cancer patient," "Other things kept making me think about cancer") and avoidant thoughts and actions ("I tried not to talk about it," "I was aware that I still had a lot of feelings about cancer, but I didn't deal with them") concerning cancer. Fifteen items are used, and women rate each event or feeling in terms of the frequency of occurrence (i.e., "not at all," "rarely," "sometimes," and "often") during the previous 7 days. Scores range from 0 to 75. For this sample, descriptive statistics were as follows: range, 0–65; mean = 26; median = 25; and standard deviation = 15.2. The scale has satisfactory reliability with internal consistency of .78–.82 and a 2-week test–retest reliability of .79–.89, respectively. The validity of the measure is suggested by data indicating that individuals who experience involuntary, distress-related thoughts following traumatic life events are also those who suffer the greatest negative effects psychologically [e.g., *(2)*].

Immune Assays

Blood cell separation. PBLs were isolated from 60 mL of venous blood by use of Ficoll gradients (Pharmacia Biotech, Inc., Piscataway, NJ). The isolated leukocytes were then washed in calcium- and magnesium-free phosphate-buffered saline and counted on a Coulter counter (Coulter Corp., Miami, FL). Aliquots of 8×10^6 isolated PBLs were suspended again in 0.8 mL of RPMI-1640 medium supplemented with 10% fetal bovine serum, 0.75% sodium bicarbonate, 2 m*M* L-glutamine, and 10 μg/mL of ciprofloxacin.

Quantification of total T lymphocytes, T-cell subsets, and NK cells. Isolated PBLs were absorbed with MAbs conjugated to either fluorescein isothiocyanate or rhodamine according to the cell surface marker being studied: total T cells (CD3, fluorescein isothiocyanate), T4 subset (CD4, rhodamine), T8 subset (CD8, fluorescein isothiocyanate), and NK cells (CD56, rhodamine). All MAbs were purchased from Coulter Corp. Briefly, 0.5×10^6 cells were incubated with the MAb for 15 minutes at room temperature. After the incubation, the cells were fixed, and the red blood cells were lysed with Optilyse C, a buffered solution containing 1.5% formaldehyde, according to the manufacturer's instructions (Coulter Corp.). Samples were analyzed with the use of a Coulter EPICS Profile II flow cytometer as described previously *(8)*.

NK cell cytotoxicity. To determine NK cell activity, a microtiter ^{51}Cr-release cytotoxicity assay was used as described previously *(9,25)*. The target cells used were K-562 cells, an NK cell-sensitive human myeloid cell line. Target cells, labeled overnight for 16 hours with ^{51}Cr, were placed in triplicate wells of 96-well V-bottom plates, and PBLs were added, resulting in effector-to-target (E:T) cell ratios of 100:1, 50:1, 25:1, 12.5:1, and 6.25:1.

NK cell response to cytokines. Procedures for treatment of PBLs with rIFN γ and rIL-2 involved preparing isolated PBLs at a concentration of 3×10^6 cells/mL in complete RPMI-1640 medium and then seeding the cells into three replicate tissue culture tubes (Falcon, Becton Dickinson and Co., Lincoln Park, NJ) at 6×10^6 cells per tube. Cells were incubated in complete RPMI-1640 medium alone or complete medium supplemented with 250 IU/mL rINF γ or 60 IU/mL rIL-2 (Genzyme, Boston, MA). Cell suspensions were gently mixed and then incubated at 37 °C in an atmosphere of 5% CO_2 for 65 hours. For the assay, triplicate aliquots of cell suspensions were placed in wells of V-bottom plates, with E:T cell ratios of 50:1, 25:1, 12.5:1, 6.25:1, or 3.13:1. In addition, six wells with target cells and medium only and target cells with detergent (5% sodium dodecyl sulfate in phosphate-buffered saline) were prepared to determine spontaneously released chromium and maximal lysis, respectively. The plates were centrifuged at 300*g* for 5 minutes at 20 °C to bring the effector and target cells into close contact; they were then incubated at 37 °C in an atmosphere of 5% CO_2 for 5 hours. After this incubation, the plates were centrifuged at 300*g* for 5 minutes at 20 °C, 100 μL of supernatant was collected from each well, and counts per minute were determined by use of a Beckman 9000 gamma counter (Beckman Instruments, Inc., Fullerton, CA) as described previously *(9,26)*.

Blastogenic response to PHA, Con A, and MAb to the T3 receptor. The concentrations for PHA and Con A used were 2.5, 5.0, and 10.0 μg/mL. To measure the blastogenic response to the MAb to the T-cell receptor, we used the following three dilutions of the purified MAb: 32:1, 64:1, and 128:1. For all three assays isolated, PBLs seeded in triplicate at 0.5×10^5 per well were incubated for 68 hours at 37 °C in 96-well flat-bottomed plates and then labeled for 4 hours with MTS, i.e., 3-(4,5-dimethylthiazol-2-yl)-5-(3-carboxymethoxyphenyl)-2-(4-sulfophenyl)-2H-tetrazolium, inner salt

(Promega Corp., Madison, WI) to measure proliferative response. Briefly, the MTS procedure is a nonradioactive calorimetric procedure that labels metabolically active cells via reduction of a colored substrate. The amount of proliferation was determined by optical density of the suspension in the well. Optical density determinations were performed by use of a Titertek Multiscan MCC microplate reader (Flow Laboratories, Inc., Finland) at a determination wavelength of 492 nm and a reference wavelength of 690 nm as has been noted *(27,28)*.

Statistical Analyses

Preliminary analyses. Before conducting the principal analyses, we checked the data for the contribution of "nuisance" variables (covariates) that could potentially be related to psychologic stress, immune outcomes, or both [*see (25)* for a discussion]. The variables examined were measures of aspirin, alcohol, caffeine, and nicotine intake; amount of sleep; plasma albumin level (as an indicator of nutritional status); incidence of recent infectious illness; and the Karnofsky performance status rating. We examined the relationships between these variables and each of the three sets of outcome variables: NK cell lysis, ability of NK cells to respond to rIFN γ and rIL-2, and the blastogenic response of PBLs to Con A, PHA, and the T3 MAb. Analysis of variance was used for the categorical independent variables, and simple correlations were used for numerically scaled independent variables.

Screening of these potential covariates involved examination of the relationships between 11 covariates and 20 dependent variables, or a total of 220 bivariate associations. Of these 220 associations, 15 were found to be statistically significant at .05 significance level. This number of significant effects is only slightly more than would be expected by chance alone (i.e., 220 × .05 = 11). Inspection of the significant relationships showed that many of them were attributable to the influence of a few outliers in the data. To be conservative, all of the regression analyses described below were run twice, once including and once excluding those covariates that had significant bivariate associations with the relevant dependent variables. In no case were results of the regression analyses significantly altered by the inclusion of the covariates. Given this fact and the consistently weak relationships of the covariates to the dependent variables, we do not report further results involving the covariates.

Principal analyses. The principal analyses assess the relationship between the IES measure of psychologic stress and the following three sets of outcome measures: 1) NK cell lysis at five E:T ratios, 2) response of NK cells to rIFN γ and rIL-2 stimulation at five E:T ratios each, and 3) the PBL blastogenic response to PHA and Con A and proliferative response to the T3 MAb at three concentrations or dilutions each.

We were interested in the role of stress in predicting these outcomes, over and above the impact of disease and recovery variables on the immune response. Thus, we chose to control for three variables: 1) age, which is associated with downregulation of the immune system; 2) disease stage, which is an indicator of the extent or burden of disease; and 3) days since surgery, which is an indicator of the degree of recovery from surgical stress and related factors (e.g., anesthesia).

Using hierarchical multiple regression *(29)*, we tested the predictive value of psychologic stress for the measured immune outcomes. This procedure enters variables in a specified sequence and, at the final step, provides a test of the variance of the dependent variable (immune outcome) due to the predictor (stress), above and beyond the contribution of the control variables (age, stage, and days since surgery). In these regression analyses, age, days since surgery, and IES were considered as numerical variables. Stage was a categorical variable with two levels: II versus III.

For all of the analyses described below, any missing data were managed by the pairwise deletion technique, wherein each bivariate association is estimated with the use of all subjects for whom measures on both variables are available. This approach allows for more complete usage of available data than do alternative procedures (e.g., listwise deletion). For all of the dependent variables except the response of NK cells to rIFN γ, the quantity of missing data was small—with never more than 10 observations missing for any bivariate association. Effective sample sizes for the regression analyses ranged from 113 for the NK cell lysis ratios to 103 for T3 MAb values. For rIFN γ measures, sample sizes varied from 85 to 49 across the range of concentrations employed.

For each analysis, we provided three regression models: models A, B, and C. Model A includes only the control (independent) variables (i.e., age, stage, and days since surgery) in predicting the immune outcome (e.g., NK cell lysis). Predictors in model A were introduced simultaneously because we had no basis for or a strong interest in investigating their effects in any particular sequence. Model B includes the three control variables as well as the psychologic stress variable (IES) in the prediction of the immune outcome. Of particular interest in this analysis was the increment in the squared multiple correlation (R^2) from model A to model B (i.e., R^2_{B-A}), indicating variance in a dependent variable (e.g., NK cell lysis) attributable to stress (IES) beyond that explained by the control predictors. In addition, the standardized regression beta (β) for the psychologic stress variable (IES) in model B (i.e., β_{Stress}) indicates the magnitude and direction of the influence of this predictor on the dependent variable. The significance of the β weight was also tested. Finally, model C indicates the contribution of psychologic stress as the lone predictor; this third model provides the simple association between psychologic stress and immune function.

Results

Analyses Predicting NK Cell Lysis

Table 1 provides the results from the three models, A, B, and C, predicting NK cell lysis. For model A, in which age, stage, and days since surgery are the independent variables, R^2_A was small and nonsignificant for every E:T ratio (all F ratios were <1.0). Because the percentage of NK cells available would influence the

Table 1. Results of regression analyses for predicting natural killer (NK) cell lysis across six effector-to-target cell (E:T) ratios

	Dependent variable: NK cell lysis at E:T ratios					
	100:1	50:1	25:1	12.5:1	6.25:1	3.125:1
Model A, R^2_A*	.005	.007	.012	.015	.020	.023
Model AA, R^2_{AA}†	.085	.148	.185	.233	.250	.241
Model B‡						
R^2_B	.135	.212	.238	.268	.275	.253
R^2_{B-AA}§	.050	.064	.053	.035	.025	.012
β_{Stress}‖	−.234	−.265	−.240	−.194	−.165	−.115
$t(df = 110)$¶	−2.462	−2.921	−2.672	−2.223	−1.892	−1.280
P	.016	.004	.008	.028	.062	.204
Model C#						
R^2_C	.067	.091	.084	.066	.056	.032
$t(df = 110)$¶	−2.826	−3.338	−3.199	−2.811	−2.558	−1.867
P	.006	.002	.002	.006	.012	.066

*Model A includes the control predictors of age, stage, and days since surgery for the immune outcome, NK cell lysis. The R^2_A is the total variance in NK cell lysis explained by these three predictors.

†Model AA includes model A variables plus the control predictor percentage of NK cells for the immune outcome, NK cell lysis. The R^2_{AA} is the total variance in NK cell lysis explained by these four predictors.

‡Model B includes model AA control variables plus the stress predictor (i.e., Impact of Event Scale [IES] score) for the immune outcome, NK cell lysis. The R^2_B is the total variance in NK cell lysis explained by the four control predictors and the stress predictor.

§R^2_{B-AA} is the increment in variance due to stress only (i.e., variance beyond that explained by the control predictors) in predicting the NK cell lysis outcome.

‖β_{Stress} is the standardized regression beta (β) for the stress variable in model B. It indicates the magnitude and direction of the influence (negative) of stress on the immune outcome.

¶df refers to the degrees of freedom in model B.

#Model C includes stress as the only predictor of the immune outcome, NK cell lysis. The R^2_C is the total variance in NK cell lysis explained by stress; this model provides the simple association between psychologic stress and immune function.

total NK cell activity as measured by lysis, we next added the percentage of NK cells, as determined by flow cytometry, into the analyses as an additional, independent control variable as shown (model AA). Across all E:T ratios, the R^2_{AA} values suggested that this variable added significant variance, as predicted, yielding R^2_{AA} values ranging from .085 to .250.

More important was the addition of the stress variable (IES) as a predictor, shown in model B. The value of R^2_B for lysis was noticeably larger than that of R^2_{AA}, and it provided a significant increment in prediction across the E:T ratios. These data indicate that the measure of psychologic stress that was used accounted for significant variance in NK cell lysis above and beyond that explained by age, stage, days since surgery, and percentage of NK cells. Moreover, the sign of the β regression coefficient for IES was negative, as predicted, indicating that an increase in measured stress was associated with a decline in NK cell lysis. The *t* tests for these coefficients were significant at five of the six E:T ratios. Also, no other predictor in model B had a significant regression coefficient.

We also provide the regression results when only IES was used as a predictor, eliminating the control predictors from the model (model C in Table 1). These results showed that the simple association between IES and NK cell lysis was statistically significant at five of the six E:T ratios.

Table 2. Results of regression analyses for predicting natural killer (NK) cell response to recombinant interferon gamma (rIFN γ) across five effector-to-target cell (E:T) ratios

	Dependent variable: NK cell response to rIFN γ at E:T ratios				
	50:1	25:1	12.5:1	6.25:1	3.125:1
Model A, R^2_A*	.025	.097	.080	.138	.124
Model B†					
R^2_B	.041	.151	.197	.257	.208
R^2_{B-A}‡	.016	.054	.117	.119	.084
β_{Stress}§	−.128	−.244	−.358	−.358	−.301
t	−1.104	−2.190	−3.203	−3.084	−2.083
df‖	82	81	74	65	46
P	.274	.032	.002	.004	.044
Model C¶					
R^2_C	.015	.077	.149	.149	.088
t	−1.128	−2.586	−3.581	−3.343	−2.080
df‖	82	81	74	65	46
P	.264	.012	.002	.002	.044

*Model A includes the control predictors of age, stage, and days since surgery for the immune outcome, NK cell response. The R^2_A is the total variance in NK cell response explained by these three predictors.

†Model B includes model A control variables plus the stress predictor (i.e., Impact of Event Scale [IES] score) for the immune outcome, NK cell response. The R^2_B is the total variance in NK cell response explained by the three control predictors and the stress predictor.

‡R^2_{B-A} is the increment in variance due to stress only (i.e., variance beyond that explained by the control predictors) in predicting the NK cell response.

§β_{Stress} is the standardized regression beta (β) for the stress variable in model B. It indicates the magnitude and direction of the influence (negative) of stress on the immune outcome.

‖*df* refers to the degrees of freedom in model B.

¶Model C includes stress as the only predictor of the immune outcome, NK cell response. The R^2_C is the total variance in NK cell response explained by stress; this model provides the simple association between psychologic stress and immune function.

Analyses Predicting Response of NK Cells to Cytokines

Results for the NK cell response to rIFN γ are provided in Table 2 and show a similar pattern. For model A, which used age, stage, and days since surgery as the independent variables, the value of R^2_A was small to moderate, ranging from .025 to .138. When stress (IES) was added to the model B regression, the R^2 values were statistically significant at all but one E:T ratio (50:1). Furthermore, the increments in the prediction due to IES, R^2_{B-A}, were significant and ranged from .054 to .119. This value reflects the proportion of variance in the cell response accounted for by stress (IES) beyond that explained by the control variables. Again, the negative weight of β for IES in model B indicated a negative influence of psychologic stress on the response of the NK cells to rIFN γ. Again, no other predictor in model B had a significant regression coefficient. Finally, the results for model C in Table 2 showed a simple association between IES and the rIFN γ response. These correlations were significant at four of the five E:T ratios; the proportions of variance accounted for were in the range of .077 to .149.

We attempted to calculate a parallel set of regressions for the response of NK cells to rIL-2. However, cells from a large proportion of the patients (62%) had no response to rIL-2. When the regressions were conducted on data obtained from the remaining patients (38%), the addition of stress (IES) in model B produced a significant R^2 value at the 25:1 E:T ratio only. It appeared that the majority of the subjects' NK cells did not respond to treatment with rIL-2.

Analyses Predicting Blastogenic Response of PBLs to Con A, PHA, and the T3 MAb

Table 3 shows regression results for the Con A and PHA blastogenic responses across three concentrations each. Because the findings are similar for both assays, they will be discussed together. For model A, which used age, stage, and days since surgery as the independent variables, the value of R^2_A for Con A ranged from .035 to .054 and was of similar magnitude for PHA, ranging from .022 to .033. Since the number of total T cells available will affect the blastogenesis values, we next added the number of T3-positive cells into the analyses as an additional, independent control variable as shown by the step model AA. Across all concentrations for each mitogen, the value of R^2_{AA} suggested that this variable added variance, yielding the R^2_{AA} values ranging from .105 to .125 for Con A and from .023 to .033 for PHA.

The addition of stress (IES) to the regression for blastogenesis added significant variance, as indicated in model B. All of the R^2 values were statistically significant. Considering the increments in R^2 due to stress (IES), these were significant and ranged from .032 to .061 for Con A and from .047 to .060 for PHA, reflecting the proportion of variance in the blastogenesis accounted for by IES beyond that explained by the control variables. Again, the negative β weights for IES in model B indicated a negative influence of psychologic stress on the blastogenic responses

Table 3. Results of regression analyses for predicting the blastogenic response to concanavalin A (Con A) and phytohemagglutinin A (PHA) across three concentrations each

	Dependent variable: blastogenic response of mitogen					
	Con A			PHA		
	10 μg/mL	5 μg/mL	2.5 μg/mL	10 μg/mL	5 μg/mL	2.5 μg/mL
Model A, R^2_A*	.035	.043	.054	.022	.024	.033
Model AA, R^2_{AA}†	.105	.125	.115	.023	.024	.033
Model B‡						
R^2_B	.166	.174	.147	.083	.074	.080
R^2_{B-AA}§	.061	.049	.032	.060	.050	.047
β_{Stress}‖	−.255	−.229	−.187	−.256	−.234	−.229
$t(df = 103)$¶	−2.668	−2.401	−1.927	−2.521	−2.299	−2.254
P	.010	.018	.058	.014	.024	.026
Model C#						
R^2_C	.053	.065	.053	.070	.054	.052
$t(df = 108)$¶	−2.443	−2.724	−2.443	−2.857	−2.489	−2.441
P	.016	.008	.016	.006	.014	.016

*Model A includes the control predictors of age, stage, and days since surgery for the immune outcome, blastogenesis. The R^2_A is the total variance in blastogenesis explained by these three predictors.

†Model AA includes model A variables plus the control predictor of number of T cells for the immune outcome, blastogenesis. The R^2_{AA} is the total variance in blastogenesis explained by these four predictors.

‡Model B includes model AA control variables plus the stress predictor (i.e., Impact of Event Scale [IES] score) for the immune outcome, blastogenesis. The R^2_B is the total variance in blastogenesis explained by the four control predictors and the stress predictor.

§R^2_{B-AA} is the increment in variance due to stress only (i.e., variance beyond that explained by the control predictors) in predicting the blastogenesis outcome.

‖β_{Stress} is the standardized regression beta (β) for the stress variable in model B. It indicates the magnitude and direction of the influence (negative) of stress on the immune outcome.

¶*df* refers to the degrees of freedom in model B.

#Model C includes stress as the only predictor of the immune outcome, blastogenesis. The R^2_C is the total variance in blastogenesis explained by stress; this model provides the simple association between psychologic stress and immune function.

across concentrations. Moreover, no other predictor in model B had a significant regression coefficient. Finally, results for model C in Table 3 showed a simple association between stress (IES) and the blastogenic response. These correlations were significant for each concentration of Con A and PHA.

Table 4 shows regression results for the proliferative response of T cells to three different dilutions of the T3 MAb. For model A, the control R^2 values were not significant for any dilution. Addition of number of T3-positive cells available as a control increased the variance accounted for as shown by the step model AA. The R^2_{AA} values ranged from .088 to .143. However, increments in R^2 due to the addition of stress (IES), as shown by R^2_{B-AA}, were significant, ranging from .056 to .067. This indicates that about 6% of the variance was accounted for by stress (IES) beyond that explained by the control variables. Once again, no other predictor in model B had a significant regression coefficient. Results for model C again showed the simple, significant association of stress (IES) with the response to the T3 MAb at all dilutions, with R^2_c values of .092 to .102.

Discussion

Any immune response involves a complex cascade of events that occur over time. Studies suggest that the peripheral products of stress can play numerous roles in regulating immunity, and so the effects of stress will, necessarily, be variable. Current research suggests, for example, that the acute stressors, both real stressors [e.g., parachute jumps *(30)*] and artificial stressors [e.g., experimental tasks including speech or math stress *(31)*], are correlated with the mobilization (increase) of NK cells. These changes are thought to be a result of alterations in cell trafficking. In contrast, studies of chronic stressors [e.g., bereavement, caregiving, or divorce *(7,9)*] suggest that stress can have an effect on the ability of NK cells to lyse a target cell, the ability of NK cells to respond to rIFN γ and rIL-2 *in vitro*, and other aspects of the cellular immune response.

Our results suggest that stress, as assessed via a self-report measure of intrusive and avoidant thoughts and behaviors about cancer, was related to a negative effect on NK cell lysis, the ability of NK cells to respond to two cytokines, the blastogenic response of PBLs to two mitogens, and the proliferative response to MAb T-cell receptor. These effects were inhibitory and of similar magnitude (i.e., reliable), both between the assays and within an assay (i.e., across E:T ratios and mitogen concentrations). The analyses controlled for variables that might also be expected to exert short-term or long-term effects on immunity—such as age, stage of disease, and days since surgery—and ruled out other potentially confounding variables (e.g., nutritional status) that might also be influential. These controls reduced the plausibility of alternative, rival hypotheses for these consistent findings.

It is recognized that NK cells mediate natural immunity, but some researchers *(32)* suggest that their role in health generally has been underestimated. For example, there is evidence to suggest that the NK cells participate either directly or indirectly in multiple developmental, regulatory, and communication networks of the immune system. Furthermore, NK cells are efficient effector cells that not only are equipped for cell killing, but also are capable of rapid responses to exogenous or endogenous signals by producing cytokines and other factors involved in interactions between immune and nonimmune cells *(20)*.

The ability to spontaneously lyse a broad range of infected cells or tumor cells is the best known functional attribute of NK cells *(20,22)*. Consistent with previous reports, these data suggest that stress may impair this important process. Our findings highlight the specific effect of cancer stress on immune function, whereas prior data obtained by Levy et al. *(33)* had suggested that women's reports of fatigue were related to lower levels of NK cell lysis. Chronically low levels of NK cell activity occur in patients with cancer, particularly when there are large tumor burdens or disseminated metastases *(32)*. In general, patients with low NK cell activity appear to be at higher risk for infections, to have more prolonged diseases, or to suffer more severe symptoms

Table 4. Results of regression analyses for predicting proliferative response of peripheral blood leukocytes to a monoclonal antibody to T-cell receptor (T3) across three dilutions

	Dependent variable: proliferative response at dilutions		
	128:1	64:1	32:1
Model A, R^2_A*	.026	.052	.064
Model AA, R^2_{AA}†	.088	.104	.143
Model B‡			
R^2_B	.155	.160	.200
R^2_{B-AA}§	.067	.056	.057
β_{Stress}‖	−.273	−.249	−.252
$t(df = 101)$¶	−2.747	−2.514	−2.604
P	.008	.014	.012
Model C#			
R^2_C	.102	.092	.094
$t(df = 101)$¶	−3.452	−3.255	−3.307
P	.002	.002	.002

*Model A includes the control predictors of age, stage, and days since surgery for the immune outcome, proliferative response. The R^2_A is the total variance in proliferation explained by these three predictors.

†Model AA includes model A variables plus the control predictor of number of T cells for the immune outcome, proliferation. The R^2_{AA} is the total variance in proliferation explained by these four predictors.

‡Model B includes model AA control variables plus the stress predictor (i.e., Impact of Event Scale [IES] score) for the immune outcome, proliferation. The R^2_B is the total variance in proliferation explained by the four control predictors and the stress predictor.

§R^2_{B-AA} is the increment in variance due to stress only (i.e., variance beyond that explained by the control predictors) in predicting the proliferation outcome.

‖β_{Stress} is the standardized beta (β) for the stress variable in model B. It indicates the magnitude and direction of the influence (negative) of stress on the immune outcome.

¶*df* refers to the degrees of freedom in model B.

#Model C includes stress as the only predictor of the immune outcome, proliferation. The R^2_C is the total variance in proliferation explained by stress; this model provides the simple association between psychologic stress and immune function.

than patients whose NK cell activity remains normal *(32,34)*.

A variety of biologic response modifiers are known to increase the activation, proliferation, or cytotoxicity of NK cells *(20)*. Among the best known activators of NK cells are IL-2 and IFN γ. Our data show that the physiologic changes associated with psychologic stress inhibited NK cell lysis. Stress also affected the ability of NK cells to respond to rIFN γ, a finding that is consistent with two previous reports involving another life stressor [i.e., caregiving for a spouse with Alzheimer's disease *(9,26)*]. It is interesting that NK cells from 62% of the women did not respond to rIL-2. In subsequent analyses comparing women who did have an rIL-2 response with those who did not, no stress or disease variable differentiated the two groups. Further studies will need to be performed to explore this result, although it is possible that the lack of responsiveness of NK cells to rIL-2 may be due to an overproduction of prostaglandin E_2 by monocytes. It has been suggested that in breast cancer patients prostaglandin E_2 decreases IL-2 production in effector cell populations, resulting in the down-regulation of the expression of the IL-2 receptor on NK cells *(23)*. Follow-up studies will need to pursue and clarify this difference in cytokine responses.

It has been shown that the ability of PBLs to respond to PHA is reduced, in general, in cancer patients *(35)*; this lowered response is related to tumor burden and declines in the ability of PBLs to respond to PHA with disease progression *(36)*. The negative effect of stress on blastogenesis was replicated in this study across two mitogens, PHA and Con A, as well as in the response of T cells to an MAb against the T-cell receptor. These findings are consistent with correlational and experimental studies indicating that stress impairs the blastogenic response of PBLs to mitogens and virus-specific T-cell responses *(8,10,37–39)*. Mitogen-induced proliferation has been used to indicate the immune system's ability to respond to antigens from pathogens. Chronically stressed, but healthy, individuals showing decrements in the cellular immune response (including NK cell lysis and the response of the PBLs to mitogens) subsequently reported a higher incidence of infectious illnesses *(8)*. If this effect is reliable, these data would suggest that cancer patients who experience high levels of stress, lowered levels of responsive T lymphocytes, and decreased NK cell function may be at greater risk for infectious illnesses as they begin adjuvant therapy.

It is interesting that evidence is accumulating to suggest that psychologic and/or behavioral stress reduction interventions may *enhance* certain aspects of the cellular immune response, including NK cell lysis. In an early investigation, Kiecolt-Glaser et al. *(40)* studied 61 healthy adults living in a retirement home. After receiving 1 month of training in progressive muscle relaxation, the subjects showed evidence of a 30% increase in NK cell lysis in comparison with those who received no treatment or only social contact. Fawzy et al. *(41)* studied 61 patients with melanoma and reported that, 6 months after treatment, subjects receiving intervention had significantly higher levels of IFN alfa-augmented NK cell activity than those who received no treatment. These data suggest that, if behavioral interventions can reduce stress and enhance the cellular immune response, then health outcomes might improve.

In conclusion, these data show a down-regulation of different aspects of the cellular immune response associated with the psychologic stress that accompanies the diagnosis and initial surgical treatment of cancer. We note that these study participants are part of a larger effort testing the biobehavioral aspects of stress, immunity, and disease course *(5)*. It will be important to document the longitudinal nature of these findings, and future studies will provide such data. Moreover, half of the women who participated have been randomly assigned to receive a psychologic/behavioral intervention specifically designed to reduce stress, enhance quality of life, and test for the biologic mechanism—such as immune responses—that may mediate any positive effects of stress reduction on health and disease outcomes.

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Notes

Supported by grants from the American Cancer Society (PBR-89); the Longaberger Company-American Cancer Society Grant for Breast Cancer Research (PBR-89A); the U.S. Army Medical Research Acquisition Activity grants (DAMD17–94-J-4165 and DAMD17–96–1–6294); Public Health Service grants R01MH51487 (National Institute of Mental Health), M01RR0034 (National Center for Research Resources), and CA16058 (National Cancer Institute), National Institutes of Health, Department of Health and Human Services; and the Department of Psychology and the College of Social and Behavioral Sciences at The Ohio State University.

We thank the participants for their assistance. In addition, we thank the following individuals for their contributions: Nicole Chaput, Angela Collier, Katheryn Pingel, Elizabeth Street, Jessica Walker, JoAnne Lester, and Beth Putz for accrual and conducting the psychologic and medical assessments; Annette Gilsey, Andrew Jackson, Bryan Laskowski, Marilyn Welt, and Susan Yep for assistance with the immune assays; and Jerry Tobler for support and comments on the manuscript.

Manuscript received May 12, 1997; revised September 25, 1997; accepted October 22, 1997.